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Local drug delivery for enhancing fracture healing in osteoporotic bone

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ABSTRACT

Fragility fractures can cause significant morbidity and mortality in patients with osteoporosis and inflict a considerable medical and socioeconomic burden. Moreover, treatment of an osteoporotic fracture is challenging due to the decreased strength of the surrounding bone and suboptimal healing capacity, predisposing both to fixation failure and non-union. Whereas a systemic osteoporosis treatment acts slowly, local release of osteogenic agents in osteoporotic fracture would act rapidly to increase bone strength and quality, as well as to reduce the bone healing period and prevent development of a problematic non-union. The identification of agents with potential to stimulate bone formation and improve implant fixation strength in osteoporotic bone has raised hope for the fast augmentation of osteoporotic fractures. Stimulation of bone formation by local delivery of growth factors is an approach already in clinical use for the treatment of non-unions, and could be utilized for osteoporotic fractures as well. Small molecules have also gained ground as stable and inexpensive compounds to enhance bone formation and tackle osteoporosis. The aim of this paper is to present the state of the art on local drug delivery in osteoporotic fractures. Advantages, disadvantages and underlying molecular mechanisms of different active species for local bone healing in osteoporotic bone are discussed. This review also identifies promising new candidate molecules and innovative approaches for the local drug delivery in osteoporotic bone.

1. Introduction

Over 10 million people in the US alone suffer from osteoporosis, which has a significant impact on fracture prevalence in the elderly [1]. Globally, the number of aged in the population is expected to double by 2040; consequently the number of osteoporotic fractures will increase greatly. The occurrence of an osteoporotic fracture can be devastating for an elderly patient, often resulting in the loss of the patient's mobility and autonomy, not to mention associated pain and increased risk of morbidity, disability and even mortality. The adverse situation can be further escalated in the case of delayed fracture healing, non-union or failure of implant fixation, often necessitating prolonged hospitalization and invasive surgery [2]. As a result, there is an increased pressure to develop combinatorial therapeutic strategies that could accelerate fracture healing and improve patients' outcomes after a fragility fracture.

The treatment of osteoporotic fractures is a challenge (Fig. 1) because of the unpredictable outcome as a result of increased bone fragility, which predisposes to a high rate of implant fixation failure and a less than optimal environment for bone formation, leading to prolonged healing time and increased risk of non-union [3–5]. In clinical practice, the fracture healing time and capacity in osteoporotic patients have not been extensively studied, but, for instance, Nikolaou et al. [5] reported delayed healing time in femoral fractures of osteoporotic patients when compared to fractures in healthy patients. Only limited clinical data is available, and therefore most of the data on osteoporotic fracture healing is based on animal studies, namely the ovariectomized (OVX) rat model. Perhaps not the perfect model to portray fragility fractures and multifactorial disorders like osteoporosis, such models have nevertheless provided valuable knowledge to the field. Studies conducted with OVX rats have demonstrated significantly reduced callus area up to 40% [4] compared to healthy controls, reduced bone mineral density and decreased mechanical properties of the callus [4,6]. Xu et al. [7] showed that the early healing period, 3–4 weeks after fracture, was impaired in OVX rats, whereas Kubo et al. [8] found changes in the later bone healing period at 12 weeks.

Fracture healing and bone repair processes have been widely studied in recent years, but less focus has been given to osteoporotic fractures. In general, the healing of an osteoporotic fracture follows the normal process of bone repair, which depends on the interplay of biomechanical, cellular and molecular factors (Fig. 2). The bone repair process is initiated by the inflammatory response and formation of fracture hematoma. The release of inflammatory,

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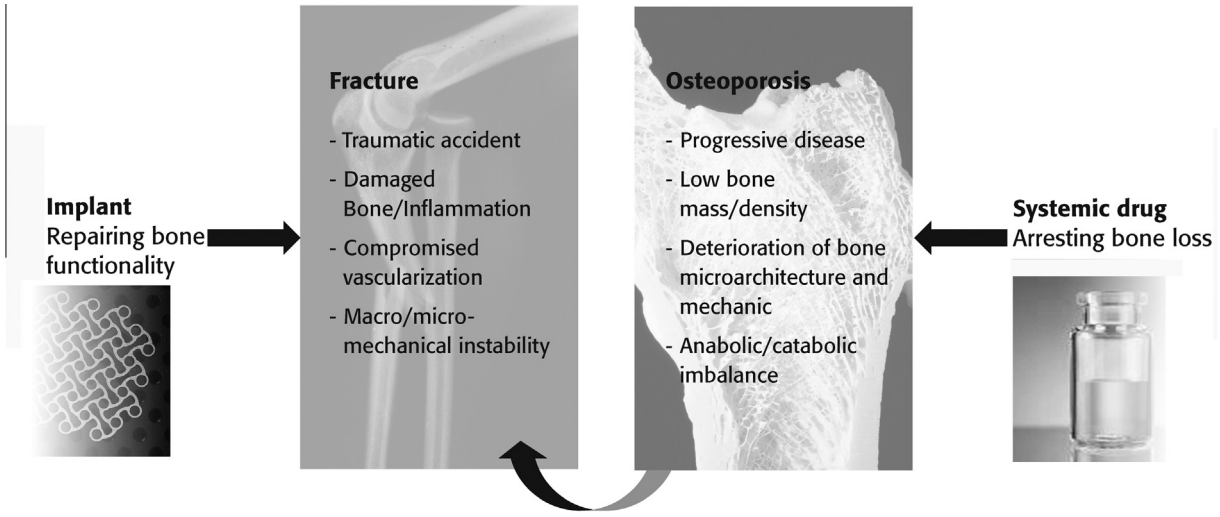

Fig. 1. The characteristics of osteoporotic bone present challenges for the management of osteoporotic fractures. Fracture healing and osteoporosis have been heavily studied research areas per se, but the effects of osteoporosis on fracture healing have been less well addressed.

growth and other regulatory factors activates mesenchymal stem cells (MSCs), which contribute to the progression of fibrocartilaginous callus into bony callus. Moreover, the fracture repair is essentially dependent on adequate stability, formation of new vasculature and remodeling of the callus by osteoclasts.

The causes behind impaired fracture healing in osteoporosis are likely to be diverse. Firstly, the mechanical stability of the osteosynthesis is compromised in osteoporotic bone, which can have serious consequences in the form of fixation failure but also more subtle effects that lead to prolonged fracture healing. The adverse structural competence of osteoporotic bone is also evident in the greatly escalated failure rate of implant fixation [2,9,10], with failure rates as high as 50% reported under osteoporotic condition [11,12]. Research for developing improved implants and technologies to allow more stable fixation in osteoporotic bone is ongoing [13].

Secondly, it is widely established that the manifestations of osteoporosis – low bone mass and impaired bone microarchitecture – are caused by an imbalance in bone resorption and formation. Age-related osteoporosis is mediated by decreased number and activity of osteoblastic cells, which leads to decline in bone formation and deterioration of bone microarchitecture. Impaired osteoblastic activity may arise from either extrinsic causes, such as abnormal signaling via systemic hormones and local growth factors, or intrinsic causes, such as apoptosis and senescence. For example, levels of various systemic hormones and factors play important roles in regulating bone remodeling, including estrogen, parathyroid hormone (PTH), calcitonin, glucocorticoids and vitamin D metabolites. In addition, alterations in the stimulatory factors released locally from bone matrix during resorption or fracture, e.g. macrophage colony-stimulating factor, transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), fibroblastic growth factors (FGF)s, bone morphogenetic proteins (BMP)s, and insulin-like growth factor (IGF)-1, can affect both osteoblast and MSC behavior. Recent studies have recognized changes in the survival, activity and function of MSCs in aged and osteoporotic bone [14–16], which could be correlated to the diminished callus formation in osteoporotic fracture.

Thirdly, the balance of inflammatory factors may be disturbed in osteoporotic bone. Pino et al. [15] reported that the concentrations of adipogenic and inflammatory factors were elevated in the bone marrow fluid of osteoporotic patients. Increased expression of pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α (TNF-α) has been associated with osteoporosis [17–19]. Although the initial inflammatory response is a natural phase of fracture healing cascade and is needed to initiate the repair process, excess and prolonged inflammatory signaling can impair callus formation and increase healing time [20].

The identification of osteopromotive and inductive agents with the potential to stimulate bone formation has raised hope for the augmentation of osteoporotic fracture healing (Table 1). Local release of bone anabolic agent in osteoporotic fracture would be aimed at rapidly increasing bone strength and quality, as well as reducing the bone healing period and preventing development of a problematic non-union (Table 2). Several growth factors possess the ability to stimulate fracture healing, potentially also under osteoporotic condition. The most extensively studied growth factors with such potential are BMP-2 and basic fibroblast growth factor (bFGF). Essentially, the success of growth factor delivery is largely dependent on an appropriate control over the spatiotemporal release. The release kinetics can influence the outcome greatly. In general, the release profile should be tailored according to the properties of the particular drug and its pharmacokinetics. The growth factor delivery is in general challenging because the sensitivity of proteins can lead to denaturation and affect their bioactivity, low availability and tissue penetration due to large molecular weight.

Due to the complications related to protein delivery, a variety of small molecules of natural or synthetic origin have been explored as a viable alternative to growth factors. By definition, small molecules are compounds of low molecular weight (<900 Da) that are able to elicit a cellular response. Small molecules can offer several advantages over large molecular weight proteins; for example, they are generally more stable, easier to process and do not denature, which makes them a cost-effective alternative to growth factors. To date, several small molecules that could be utilized in healing of osteoporotic bone fractures have been identified, including simvastatin, strontium ranelate, prostaglandin E_2 (PGE_2) receptor agonists, icariin and melatonin. Despite the promising results obtained so far, for many of them the optimal dose, possible toxicity and effective delivery strategies require more careful investigation.

This review aims to provide an overview on local drug delivery in the context of osteoporotic fractures. Selections of representative drugs that have been investigated for local delivery in fracture healing and considered for osteoporotic bone are reported. Given the recent advances in the biomaterial and drug delivery field, combining these agents with a suitable delivery strategy presents an approach ideally suited to advancing the clinical management of osteoporotic fractures and meeting the challenges presented

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