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Review

Controlling the biological function of calcium phosphate bone substitutes with drugs

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ABSTRACT

There is a growing interest in bone tissue engineering for bone repair after traumatic, surgical or pathological injury, such as osteolytic tumor or osteoporosis. In this regard, calcium phosphate (CaP) bone substitutes have been used extensively as bone-targeting drug-delivery systems. This localized approach improves the osteogenic potential of bone substitutes by delivering bone growth factors, thus extending their biofunctionality to any pathological context, including infection, irradiation, tumor and osteoporosis. This review briefly describes the physical and chemical processes implicated in the preparation of drug-delivering CaPs. It also describes the impact of these processes on the intrinsic properties of CaPs, especially in terms of the drug-release profile. In addition, this review focuses on the potential influence of drugs on the resorption rate of CaPs. Interestingly, by modulating the resorption parameters of CaP biomaterials, it should be possible to control the release of bone-stimulating ions, such as inorganic phosphate, in the vicinity of bone cells. Finally, recent in vitro and in vivo evaluations are extensively reported.

1. Introduction

Calcium phosphate (CaP) is the main component of bone and is a biocompatible and biodegradable biomaterial. For these reasons, it has been widely used as a bone substitute for bone reconstructive surgery [1]. CaP is efficacious in most non-load-bearing clinical situations, including orthopedics, and dental, ear, nose and throat surgeries. Today, there is major interest in improving the biological function of CaP for bone reconstructive surgery. This includes (i) optimizing its osteogenic potential through the release of growth factors involved in bone regeneration; and (ii) extending its biofunctionality to provide a bone response in pathological situations, such as bone infection, osteoporosis and bone tumor [2].

In this regard, CaP biomaterials, mainly ceramics, cements, composites and thin coatings, seem to be attractive candidates as bioactive carriers. In situ delivery of therapeutic agents (TAs) from CaPs provides a specific tissue response and guarantees optimal bioavailability. In addition, thanks to the localized delivery, the desired drug concentration can be maintained, even in inaccessible bone sites or after bone structure modification due to surgery. Moreover, bioavailability is considered to be optimal, thanks to the direct in situ TA release, because the dose and frequency of administration can be reduced, resulting in fewer side effects. Improving treatment tolerance is critical to optimize patient compliance and persistence and, consequently, therapeutic efficacy. Indeed, long-term treatments are unfortunately frequently associated with poor adherence, because of constraints related to drug administration or the occurrence of side effects, thus jeopardizing the overall treatment success [3].

The first part of this review focuses on the properties required for CaP biomaterials to be effective as drug-delivery systems. The second part describes the physical and chemical processes involved in the preparation of drug-delivering CaPs and their impact on the intrinsic properties of CaPs, especially in terms of the drug-release profile. This part also focuses on determining whether it might be possible to modulate the resorption of CaPs with drugs and that in turn could control the release of physiological ions, such as inorganic phosphate (Pi), which are known for their bone-stimulating properties. Finally, the last part reports recent biological evaluations performed on these bone-targeting drug-delivery systems in the context of bone regenerative surgery.

2. CaP as an "active" vector

CaP materials are considered to be the best alternative to bone grafting because of their chemical properties, which are suitable for bone remodeling [4–9]. CaP exists in different forms, such as powders, granules, blocks, ceramics, cements and coatings, which can be selected depending on the bone defect to be repaired.

2.1. Ceramics and unsintered apatites

Several synthetic types of CaPs are widely used as bone substitutes, including hydroxyapatite (HA), $Ca_{10}(PO_4)_6(OH)_2$,

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