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Review

Controlling the biological function of calcium phosphate bone substitutes with drugs

E. Verron *, J.M. Bouler, J. Guicheux

INSERM U791, Faculté de Chirurgie Dentaire, 1 place Alexis Ricordeau, Université de Nantes, 44042 Nantes, France

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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), $Ca_{10}(PO_4)_6(OH)_2$,

* Corresponding author. Tel.: +33 2 40 41 29 16; fax: +33 2 40 08 37 12.
E-mail address: elise.verron@univ-nantes.fr (E. Verron).

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beta-tricalcium phosphate (β-TCP), $Ca_3(PO_4)_2$, HA/β-TCP mixtures, and unsintered apatite or calcium-deficient apatite (CDA). These CaPs must be sintered at temperatures higher than 1100 °C. Their composition and structure condition their solubility [10]; the comparative extent of dissolution is α-TCP ≫ CDA > β-TCP ≫ HA. On one hand, thanks to their microporosity (pore size <10 μm), these CaPs can be impregnated with biological fluids, which increases their surface dissolution [11,12]. On the other hand, their macroporosity, defined as a pore size larger than 80–100 μm, conditions the colonization with bone cells and can be modulated by the addition of organic substances, such as naphthalene or sucrose particles, that are sublimated or calcinated before sintering [13]. The solubility, and biological and mechanical properties of these ceramics depend strongly on the size of the crystal, the presence of ionic impurities, the specific surface area, and their macroporosity and microporosity [12,14,15].

2.2. Cements

The development of CaP cements (CPCs), based on studies performed originally by LeGeros in 1982 [16] and Brown and Chow in 1986 [17], has revolutionized the world of bone tissue engineering. The major advantage of CPCs is their ability to easily adapt to the shape of the bone defect [18,19]. Indeed, thanks to their moldability, CPCs can fit perfectly into the implant site, thus optimizing bone–biomaterial contact, even in geometrically complex bone defects. CPCs are considered to be the most promising materials for minimally invasive surgery. After implantation into the bone defect, CPCs are able to self-set [20] and harden without any exothermic reaction that could be prejudicial to the bone tissue and/or loaded drug. CPCs rapidly integrate into the bone structure and are then progressively resorbed, mainly by cellular processes. Apatite cements are constituted by entangled microcrystals that are more similar to biological apatites in size and composition than to HA ceramic particles [18,21,22].

However, CPCs present several limitations, such as their slow in vivo biodegradation and poor mechanical properties, although these properties are better than those of ceramics. CPCs remain too dense after implantation; thus, their low macroporosity does not allow for 3-D cell colonization and tissue ingrowth. In this regard, the incorporation of resorbable fibers or particles into CPCs should develop channels suitable for bone ingrowth after their dissolution [23,24]. Nevertheless, both their mechanical and osteoconductive properties presently remain non-optimal. Recently, a study compared three different strategies to create porosity: (i) by the creation of CO_2 bubbles during setting; (ii) by the incorporation of poly(lactic-co-glycolic acid) (PLGA) microspheres; and (iii) by the incorporation of either hollow or dense degradable PLGA microspheres (CPC-hPLGA and CPC-dPLGA) [25]. Each method allowed for the obtention of an interconnected porous structure with a final porosity greater than 70% (v/v).

2.3. Requirements for effective drug delivery by biomaterials

The properties required of a biomaterial to be effective for the delivery of drugs to bones remain the subject of extensive research. Biomaterial-based drug-delivery systems require properties critical for bone tissue engineering, such as biocompatibility, osteoconductivity, and lack of cytotoxicity and immunogenicity to avoid any adverse reactions in cellular and tissue environments [18]. The properties of biomaterials in terms of drug adsorption depend largely on their microstructure (i.e. specific surface area, porous architecture (size distribution, connectivity), roughness, grain size, etc.) [26]. These parameters depend on the processing conditions, such as the liquid/powder ratio, the size of particles and the shape of the starting powder [27]. In addition, the structure of a biomaterial (macro- and microporosity) also affects its resorption after dissolution or/and cellular processes, and therefore greatly influences the drug-release profile. One of the most difficult challenges for a drug-carrier biomaterial is to maintain a sufficient mechanical stability, i.e. similar to bone tissue, while exhibiting an appropriate macroporosity for cellular infiltration and bone ingrowth. Furthermore, the degradation of the carrier and sterilization step should not produce toxic metabolites or degrade the loaded drug. Finally, the biomaterial should be available in various forms in terms of shape, size and structure, to be relevant for clinical applications [19]. Fig. 1 summarizes the general properties required of a biomaterial-based drug-delivery system for use in bone tissue engineering.

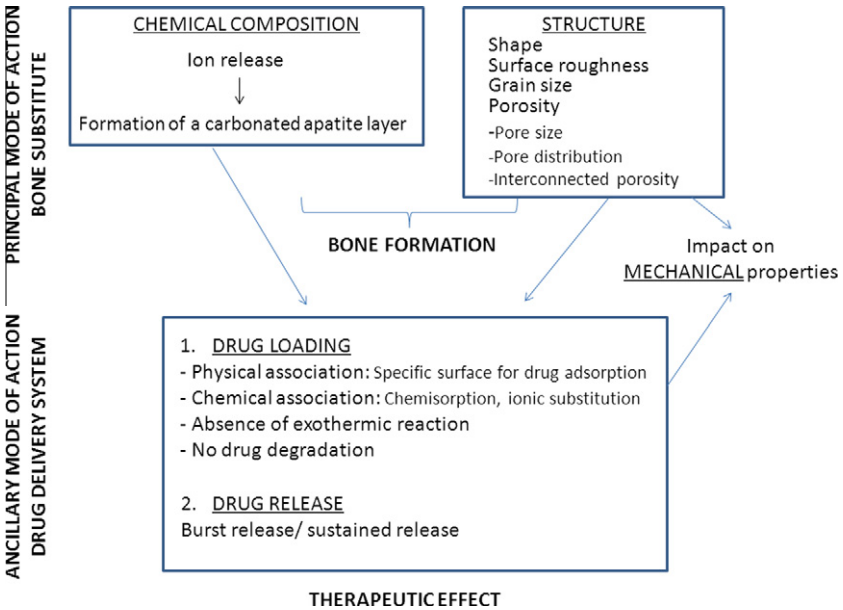

Fig. 1. Requirements for effective drug delivery by bone substitutes.