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Review

Current views on calcium phosphate osteogenicity and the translation into effective bone regeneration strategies

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ABSTRACT

Calcium phosphate (CaP) has traditionally been used for the repair of bone defects because of its strong resemblance to the inorganic phase of bone matrix. Nowadays, a variety of natural or synthetic CaP-based biomaterials are produced and have been extensively used for dental and orthopaedic applications. This is justified by their biocompatibility, osteoconductivity and osteoinductivity (i.e. the intrinsic material property that initiates *de novo* bone formation), which are attributed to the chemical composition, surface topography, macro/microporosity and the dissolution kinetics. However, the exact molecular mechanism of action is unknown. This review paper first summarizes the most important aspects of bone biology in relation to CaP and the mechanisms of bone matrix mineralization. This is followed by the research findings on the effects of calcium (Ca^{2+}) and phosphate (PO_4^{3-}) ions on the migration, proliferation and differentiation of osteoblasts during in vivo bone formation and in vitro culture conditions. Further, the rationale of using CaP for bone regeneration is explained, focusing thereby specifically on the material's osteoinductive properties. Examples of different material forms and production techniques are given, with the emphasis on the state-of-the art in fine-tuning the physicochemical properties of CaP-based biomaterials for improved bone induction and the use of CaP as a delivery system for bone morphogenetic proteins. The use of computational models to simulate the CaP-driven osteogenesis is introduced as part of a bone tissue engineering strategy in order to facilitate the understanding of cell–material interactions and to gain further insight into the design and optimization of CaP-based bone reparative units. Finally, limitations and possible solutions related to current experimental and computational techniques are discussed.

1. Introduction

Bone is a dynamic, highly vascularized and mineralized tissue that has self-remodelling and healing capacities under normal physiological conditions, with bone loss due to disuse and upon injury. It provides structural support to the body for locomotion, serves as a protective cage for internal organs, and is a site for haematopoiesis and endocrine regulation. It also maintains the acid–base balance of blood, and serves as storage for minerals (mainly calcium (Ca^{2+}) and phosphate (PO_4^{3-})) and growth factors that are essential for vital physiological events, such as ion homeostasis and other intracellular signalling pathways.

In fact, bone is a biocomposite tissue consisting of an organic phase (mainly collagen type-1 fibres, ~20%) and an inorganic phase (mainly carbonated hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$), (~60%) [1] (Fig. 1A) that are organized in a lamellar cylindrical osteon system (i.e. the compact bone) or present as irregular thin trabecular plates and struts (i.e. the spongy bone) [2]. This special organization of collagen fibres and mineralized matrix (deposited by the bone-forming cells, i.e. the osteoblasts) renders the bone tissue with relatively high elastic modulus and compressive strength, but low tensile and shear strength [3,4] (Fig. 1B). These mechanical properties are dependent on the anatomic location [5,6], and are influenced among others by the porosity and percentage of the mineral content within a bone tissue to suit a particular functionality (e.g. 80% mineral content within ossicles for sound transduction

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