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The influence of genetic factors on the osteoinductive potential of calcium phosphate ceramics in mice

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ABSTRACT

The efficacy of calcium phosphate (CaP) ceramics in healing large bone defects is, in general, not as high as that of autologous bone grafting. Recently, we reported that CaP ceramics with osteoinductive properties were as efficient in healing an ilium defect of a sheep as autologous bone graft was, which makes this subclass of CaP ceramics a powerful alternative for bone regeneration. Although osteoinduction by CaP ceramics has been shown in several large animal models it is sporadically reported in mice. Because the lack of a robust mouse model has delayed understanding of the mechanism, we screened mice from 11 different inbred mouse strains for their responsiveness to subcutaneous implantation of osteoinductive tricalcium phosphate (TCP). In only two strains (FVB and 129S2) the ceramic induced bone formation, and in particularly, in FVB mice, bone was found in all the tested mice. We also demonstrated that other CaP ceramics induced bone formation at the same magnitude as that observed in other animal models. Furthermore, VEGF did not significantly increase TCP induced bone formation. The mouse model here described can accelerate research of osteoinductive mechanisms triggered by CaP ceramics and potentially the development of therapies for bone regeneration.

1. Introduction

Porous calcium phosphate ceramics are frequently used in orthopaedic surgery as graft material to heal bone defects. Their chemical composition is similar to the natural mineral of the bone. In general, CaP ceramics are considered osteoconductive, meaning that they are able to facilitate bone infiltration from the bone surrounding the defect. A subclass of CaP ceramics also has been recognized as being osteoinductive [1–5]. We define osteoinductivity of a biomaterial by the potential of the material to induce bone formation while implanted in an animal at ectopic sites (e.g. subcutaneously or intramuscularly). The specific biological response triggered by osteoinductive materials that results in bone formation is, however, poorly known. Nonetheless, their osteoinductive capacity has been often linked with specific physico-chemical properties such as chemical composition, scaffold architecture and micro- and nano- structure.

We recently reported that ceramics with different physico-chemical properties induce bone formation in dogs with different degrees of efficacy: tricalcium phosphate (TCP) induced more bone formation than hydroxyapatite (HA). In the same study, we also demonstrated that TCP grafting of an ilium defect in sheep is as effective as the most frequently used therapies for human patients: autologous bone grafting and recombinant human BMP-2 (rhBMP-2). This finding strongly revealed the potential of osteoinductive ceramics to heal bone defects in clinical scenarios, overcoming the disadvantages of donor tissue morbidity and pain associated with autologous bone graft and issues related to cost and safety associated with the use of rhBMP-2 [6]. However, in order to bring these materials to the clinic, full understanding of the mechanism of action would help to determine their efficacy, efficiency and safety.

The immune system has been associated with the physiological response leading to CaP ceramic induced bone formation. It is hypothesized, for instance, that materials with different surface

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