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Acidic peptide hydrogel scaffolds enhance calcium phosphate mineral turnover into bone tissue

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ABSTRACT

Designed peptides may generate molecular scaffolds in the form of hydrogels to support tissue regeneration. We studied the effect of hydrogels comprising β-sheet-forming peptides rich in aspartic amino acids and of tricalcium phosphate (β-TCP)-loaded hydrogels on calcium adsorption and cell culture in vitro, and on bone regeneration in vivo. The hydrogels were found to act as efficient depots for calcium ions, and to induce osteoblast differentiation in vitro. In vivo studies on bone defect healing in rat distal femurs analyzed by microcomputerized tomography showed that the peptide hydrogel itself induced better bone regeneration in comparison to non-treated defects. A stronger regeneration capacity was obtained in bone defects treated with β-TCP-loaded hydrogels, indicating that the peptide hydrogels and the mineral act synergistically to enhance bone regeneration. In vivo regeneration was found to be better with hydrogels loaded with porous β-TCP than with hydrogels loaded with non-porous mineral. It is concluded that biocompatible and biodegradable matrices, rich in anionic moieties that efficiently adsorb calcium ions while supporting cellular osteogenic activity, may efficiently promote β-TCP turnover into bone mineral.

1. Introduction

Bone is a composite biomaterial that functions as a connective tissue responsible for the mechanical support of muscular activity. Its extracellular matrix (ECM) has a unique composition of calcium phosphate minerals, primarily in the form of hydroxyapatite, which provide strength and support to the bone tissue.

Designed biomaterials play an important role in tissue engineering, as they provide controllable environments for supporting cellular regenerative functions [1]. In recent years, significant progress has been made in the development of synthetic bone graft materials, including bioceramics, biopolymers and composite materials, which share the benefits of being synthetic and amenable to design and modification to meet different needs [2–4]. Moreover, synthetic materials have been shown to enhance bone growth, a property that has been linked to their stimulatory effect on cellular activity.

Indeed, the resorption of synthetic bone graft minerals has been reported to affect cell proliferation and to provide space for tissue growth [5]. However, despite the immense progress achieved by tissue engineering studies, autologous bone grafts are still considered the "gold standard" in bone defect treatments [6]. These procedures are unavoidably associated with limitations to the extent of tissue possible to harvest, augmented morbidity and postoperative complications [7]. Allografts and xenografts of bone tissue also suffer from constraints, such as the risks associated with host immune response and the transfer of pathogens [8].

Calcium phosphate minerals, extensively studied in the context of bone regeneration, exist in various forms, ranging from hydroxyapatite to amorphous calcium phosphate, which are the most and least thermodynamically stable phases, respectively [9,10]. In these systems, bone regeneration depends, among other properties, on the mineral's dissolution rate particle size, crystallinity and porosity [11,12], and on the cells in the proximity of the mineral [13,14]. Minerals that dissolve over time are considered superior to the hydroxyapatite form, which remains essentially intact in the regrown bone, limiting the ability of the tissue to fully regenerate [15,16]. Biodegradable ceramics may have the ability to mechanically support bone voids while resorbing over time and providing space for the simultaneous growth of new bone [17].

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