Effect of strontium-substituted biphasic calcium phosphate on inflammatory mediators production by human monocytes

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Abstract

Calcium phosphate materials are widely used as bone substitutes because of their properties close to those of the mineral phase of bones. Nevertheless, after several months, calcium phosphate-based materials release particles that may be phagocytosed by monocytes, leading to an inflammatory reaction. Strontium is well known to counteract the osteoporosis process, but little is known about its effect on inflammatory processes. The purpose of this work was to study the effect of biphasic calcium phosphate (BCP) particles substituted with strontium on the inflammatory reaction. Human primary monocytes stimulated or not by lipopolysaccharide (LPS) were exposed to BCP particles containing strontium for 6 and 24 h. Inflammatory mediators (cytokines and matrix metalloproteinases (MMPs)) production was then quantified by ELISA and zymography. We observed that the presence of strontium had few effects on unstimulated cells, but it decreased the production of pro-inflammatory cytokines and the chemokine interleukin 8 in LPS-stimulated cell-conditioned medium. This work suggests for the first time that strontium may be involved in the control of inflammatory processes following BCP phagocytosis by human monocytes.

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1. Introduction

Calcium phosphate materials, and especially hydroxyapatite (HA), are widely used as biomaterial to fill bone defects or to coat metal parts of prostheses, thanks to their similarity with the inorganic phase of bone. The early dissolution of the amorphous phase of the coating during the bone remodeling leads to the release of calcium phosphate particles having various characteristics and compositions [1–3], even when dense material is used [4]. A major concern regarding these wear debris is their implication in aseptic implant loosening [5]. Monocytes/macrophages are commonly observed at the interface between biomaterials and host tissue. They are among the first cells to colonize the inflammatory site and they play a key role in the immune response to foreign bodies [6–8]. It has been demonstrated that the interaction between HA particles and human monocytes leads to the release of inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) [9] and IL-18 [10]. Anti-inflammatory cytokines such as IL-10 are also produced [9], and have been shown to inhibit IL-6 and TNF-α production following phagocytosis of polymethylmethacrylate particles by monocytes/macrophages [11]. Moreover, monocytes have been shown to produce matrix metalloproteinases (MMPs) at the bone/prosthesis interface [12,13]. MMPs belong to a zinc-dependent proteinase family with more than 25 members, secreted as inactivezymogens [14] and largely involved in extracellular matrix (ECM) proteolytic degradation. This ECM proteolysis is responsible in part for bone degradation as a result of an imbalance between levels of tissue inhibitors of metalloproteinases (TIMPs) and MMP activators.

Previous studies have shown that zinc-substituted HA had a favourable effect on the production of cytokines by human monocytes [15] and polymorphonuclear neutrophils (PMNs) [16,17]. Indeed it decreases the inflammatory and chemotactic mediators production, and MMP-9 activity related to HA particle phagocytosis by human PMNs. Moreover, zinc inhibits MMP-2 production by human gingival tissue [18].