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Silicate bioceramics induce angiogenesis during bone regeneration

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ABSTRACT

The capacity to induce rapid vascular ingrowth during new bone formation is an important feature of biomaterials that are to be used for bone regeneration. Akermanite, a Ca-, Mg- and Si-containing bioceramic, has been demonstrated to be osteoinductive and to promote bone repair. This study further demonstrates the ability of akermanite to promote angiogenesis and investigates the mechanism of this behavior. The akermanite ion extract predominantly caused Si-ion-stimulated proliferation of human aortic endothelial cells. The Si ion in the extract was the most important component for the effect and the most effective concentration was found to be 0.6–2 μg ml^{-1}. In this range of Si ion concentration, the stimulating effect of the ceramic ion extract was demonstrated by the morphology of cells at the primary, interim and late stages during in vitro angiogenesis using ECMatrix™. The akermanite ion extract up-regulated the expression of genes encoding the receptors of proangiogenic cytokines and also increased the expression level of genes encoding the proangiogenic downstream cytokines, such as nitric oxide synthase and nitric oxide synthesis. Akermanite implanted in rabbit femoral condyle model promoted neovascularization after 8 and 16 weeks of implantation, which further confirmed its stimulation effect on angiogenesis in vivo. These results indicate that akermanite ceramic, an appropriate Si ion concentration source, could induce angiogenesis through increasing gene expression of proangiogenic cytokine receptors and up-regulated downstream signaling. To our knowledge, akermanite ceramic is the first Si-containing ceramic demonstrated to be capable of inducing angiogenesis during bone regeneration.

1. Introduction

Vascularization is critical for bone regeneration. Implants carrying proangiogenic genes and cells have been shown to induce bone vessel growth [1–5]. Osteogenesis and osteoinductivity, including Haversian canal formation, have been observed in calcium phosphate (β-TCP) implants, suggesting that bioceramics might play a critical role in angiogenesis during bone regeneration [6,7]. Further studies on bioactive glasses have demonstrated the existence of ionic dissolution products of the silicate-based biomaterial-stimulated gene expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in fibroblasts, implying a potential for angiogenic induction by this kind of silicate material [8–10].

Akermanite ($Ca_2MgSi_2O_7$), a Mg-containing silicate bioceramic, has been found to be degradable and biocompatible [11], and able to stimulate proliferation of osteoblasts [12] and bone marrow mesenchymal stem cells (MSCs) [12,13]. Moreover, akermanite has also been found to stimulate expression of osteogenic marker genes in human bone MSCs and human adipose-derived stem cells (hASCs), and enhance in vivo bone regeneration as compared with the β-TCP bioceramics [12–15]. However, it is unknown whether akermanite can induce angiogenesis, which may contribute to enhancing osteogenesis.

Angiogenesis involves endothelial cell proliferation, migration and tube formation, which is regulated by several angiogenic growth factors such as VEGF, bFGF and transforming growth factor-β (TGF-β) [1–3,16–19]. Similarly, the receptors (R), VEGFR, FGFR and TGFβR, on the surface of endothelial cells are also believed to regulate angiogenesis in vivo [20–22]. Proangiogenic factors bind to their receptors, resulting in the expression of nitric

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