Osteostatin-loaded onto mesoporous ceramics improves the early phase of bone regeneration in a rabbit osteopenia model

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Abstract
Parathyroid hormone-related protein (PTHrP) is an important modulator of bone formation. Recently, we reported that PTHrP (107–111) (osteostatin) coating onto mesoporous ceramics confers osteogenic activity to these materials. Bone repair is dramatically compromised in osteopenia/osteoporosis. Thus, we examined the efficacy of unmodified and organically modified SBA15 ceramics loaded with osteostatin in promoting bone repair in an osteoporotic rabbit model. Osteoporosis was induced in New Zealand rabbits by methylprednisolone administration, and healthy rabbits were used as controls. Tested materials were implanted into a femoral cavitory defect, and animals were sacrificed at 2 weeks post-implantation. At this time, implants were encapsulated by a variable layer of fibrotic tissue with no evidence of inflammation. Similarly to observations in normal rabbits, both types of osteostatin-loaded bioceramics induced tissue regeneration associated with increased staining for PCNA, Runx2, osteopontin, and/or vascular endothelial growth factor in osteoporotic rabbits. Our present findings demonstrate that these osteostatin-bearing bioceramics increase the early repair response not only in normal bone but also in osteoporotic bone after a local injury.

1. Introduction
Bone repair to reconstitute skeletal integrity begins immediately after trauma. The healing events involve a hematoma-related infiltration of inflammatory cells, which increases the local delivery of cytokines at the site of damage, promoting both the recruitment and growth of mesenchymal stem cells from the periostial cambium [1,2]. These cells then respond by committing to the chondrogenic or osteogenic lineage, depending on whether vascularization is disrupted (close to the bone disjunction) or better preserved, respectively; the latter process is also favoured by the mechanical stability of the injured bone. Thus, the repair process is classically thought to involve both intramembranous and endochondral ossification followed by osteoclast-directed remodelling [3]. Recent evidence also supports the notion that at an early stage during bone regeneration, recruitment of stromal cells may activate osteoclastogenesis and osteoclast-mediated resorption of damaged bone. This sets the conditions for new bone formation in a way that mimics bone remodelling within the basic multicellular units in the bone surface [4,5].

Knowledge of the molecular pathways and factors implicated in bone regeneration after skeletal trauma is still limited. However, the important roles played by bone morphogenetic proteins (BMPs), namely BMP-2 [2,6], and, as shown more recently, by Wnt/β-catenin pathway factors [7], in this regard provide a molecular rationale for using these factors as osteoinductive therapies. Injured bone tissue revascularization is a source of oxygen, nutrients and cell precursors, and thus is critical for successful bone repair. This is mainly carried out by the production of vascular endothelial growth factor (VEGF) in response to BMPs and other local factors in the callus, establishing the basis for VEGF administration as a putative therapy to enhance skeletal healing [8,9]. Other factors such as interleukins-1 and -6 and receptor activator of NF-κB ligand have an important role in osteoclast recruitment and newly formed bone remodelling [5,10].