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Cell Therapy of Bone

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INTRODUCTION: We recently reported the 7 year follow-up repair of large bone defects in humans by autologous in vitro expanded bone marrow stromal cells (BMSC) seeded onto a 100% HA porous ceramic. Despite the success of the bone repair we failed to observe complete bone regeneration due the low resorbability of the porous HA bioceramics. In the attempt to improve the tissue engineering approach, we tested in vitro and in two animal models a new resorbable porous scaffold, based on silicon-stabilized tricalcium phosphate ceramic biomaterial.

METHODS: *Sheep model***:** Critical size defects of the tibial mid diaphysis of sheep were treated with autologous bone (control group) or with the ceramic scaffold seeded or not with expanded BMSC. An internal locking plate was applied for stabilization. Animals were sacrificed at different times during the 10-months follow-up period. To determine bone and scaffold percentages, tissue morphology, and vascular density, radiography, microradiography and histology were performed.

RESULTS: In the autologous bone group new bone synthesis was already observed in the first follow-up radiographs, but stopped after 20-24 weeks from surgery reaching only 70-80% of the normal bone value. No bone formation occurred in implants not seeded with cells. A bone deposition occurred in the cell-seeded scaffolds starting from the periphery of the bone stumps where a higher vascular density was observed. This effect ended within 20-24 weeks, as for the autologous bone, suggesting similar kinetics of the repair processes involved. BMSC-loaded ceramics displayed a progressive scaffold resorption, coincident with new bone deposition.

To investigate the coupled mechanisms of bone formation and scaffold resorption, X-ray computed microtomography with synchrotron radiation (μCT) was performed on BMSC-seeded ceramic cubes before and after implantation in immunodeficient mice for 2 or 6 months. All scaffolds presented a uniform density before implantation. After being seeded with cells and their in vivo implantation, the *same scaffolds* presented a decreased scaffold trabecular thickness and areas of different segregated densities. A μX-ray diffraction analysis performed on sections of the same samples revealed that in the contact areas between the newly formed bone and the scaffold, the TCP component of the ceramic decreased much faster than the HA component. In scaffolds implanted without cells, both the ceramic density and the TCP:HA ratio remained unchanged with respect to the pre-implantation analysis

DISCUSSION & CONCLUSIONS: The, porous ceramic implants, based on silicon-stabilized tricalcium phosphate combines good osteoconductive properties with the capability to be progressively resorbed during the bone repair/regeneration process. The coupling between scaffold resorption and bone formation is new and it is at variance to the results with other bone biomaterials that are either minimally resorbed in vivo, as hydroxyapatite, or more soluble one, as beta-TCP or bioglasses that may dissolve in vivo before bone formation and a proper tissue repair.

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