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Piled Critical Size Bone-Biomimetic and Biominerizable Nanocomposites: Formation of Bioreactor-Induced Stem Cell Gradients under Perfusion and Compression

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Abstract : Perfusion bioreactors are used to solve problems in tissue engineering in terms of sufficient nutrient and oxygen supply. Such problems especially occur in critical size grafts because vascularization is often too slow after implantation ending up in necrotic cores. Biominerizable and biocompatible nanocomposite materials are attractive and suitable scaffold materials for bone tissue engineering because they offer mineral components in organic carriers – mimicking natural bone tissue. In addition, human adipose derived stem cells (ASCs) can potentially be used to increase bone healing as they are capable of differentiating towards osteoblasts or endothelial cells among others. In the present study, electrospun nanocomposite disks of poly-lactic-co-glycolic acid and amorphous calcium phosphate nanoparticles (PLGA/a-CaP) were seeded with human ASCs and eight disks were stacked in a bioreactor running with normal culture medium (no differentiation supplements). Under continuous perfusion and uniaxial cyclic compression, load-displacement curves as a function of time were assessed. Stiffness and energy dissipation were recorded. Moreover, stem cell densities in the layers of the piled scaffold were determined as well as their morphologies and differentiation status (endothelial cell differentiation, chondrogenesis and osteogenesis). While the stiffness of the cell free constructs increased over time caused by the transformation of the a-CaP nanoparticles into flake-like apatite, ASC-seeded constructs showed a constant stiffness. Stem cell density gradients were histologically determined with a linear increase in the flow direction from the bottom to the top of the 3.5 mm high pile ($r2 > 0.95$). Cell morphology was influenced by the flow rate, with stem cells getting more roundish at higher flow rates. Less than 1 % osteogenesis was found upon osteopontin immunostaining at the end of the experiment (9 days), while no endothelial cell differentiation and no chondrogenesis was triggered under these conditions. All ASCs had mainly remained in their original pluripotent status within this time frame. In summary, we have fabricated a critical size bone graft based on a biominerizable bone-biomimetic nanocomposite with preserved stiffness when seeded with human ASCs. The special feature of this bone graft was that ASC densities inside the piled construct varied with a linear gradient, which is a good starting point for tissue engineering interfaces such as bone-cartilage where the bone tissue is cell rich while the cartilage exhibits low cell densities. As such, this tissue-engineered graft may act as a bone-cartilage interface after the corresponding differentiation of the ASCs.

Keywords : bioreactor, bone, cartilage, nanocomposite, stem cell gradient
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