Dissertation Abstract

Osteon-Mimetic Nanocomposite Materials for Bone Regeneration

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The limitations of large bone defect regeneration has brought the focus of Bone Tissue Engineering research on fabricating three-dimensional bone-mimetic grafts that could enhance osteogenesis and vascularization. Osteons composed of apatite-deposited aligned collagen nanofiber layers are the fundamental building blocks of cortical bone. In natural cortical bone, mineralization is mediated by extracellular matrix (ECM) proteins with amino acid sequences rich in glutamic acid. This dissertation is focused on the establishment of a novel biomimetic approach to engineer scaffolds for healing large bone defects.

In the first part, we investigated the effect of calcium phosphate (CaP) deposition on aligned surface-modified nanofibers (NF) with a glutamic acid peptide (GLU-NF) on osteogenic differentiation of marrow stromal cells (MSCs). In order to mimic the morphology of the bone ECM, the EEGGC peptide (GLU) with two glutamic acid residues was conjugated to a low molecular weight polylactide (PLA) macromer. The synthesized PLA-GLU polymer-peptide conjugate was blended with high molecular weight poly(lactide-co-glycolide) (PLGA) and electrospun to form GLU-NF. GLU-NF microsheets were incubated in a modified simulated body fluid (SBF) for nucleation and growth of CaP crystals on the fiber surface. To achieve a high CaP to fiber ratio, a layer-by-layer (LBL) approach was used to improve diffusion of calcium and phosphate ions inside the microsheets. Results demonstrate that surface modification of aligned synthetic NF with EEGGC peptide significantly increased nucleation and growth of CaP crystals on the fibers, leading to increased mechanical properties and osteogenic
differentiation of MSCs. In addition, CaP to fiber ratios as high as 200%, which lie between those of cancellous (160%) and cortical (310%) bone, were obtained with the LBL approach.

In the second part, the perforated CaP deposited NF microsheets were used to fabricate osteon-mimetic microtubes. The effect of the microtubular structure of CaP-deposited NF scaffolds on osteogenesis of MSCs and vascularization of endothelial progenitor cells (EPCs) and MSC co-cultures was investigated. It was found that microtubular scaffolds preferentially supported osteogenic and vasculogenic differentiation of MSCs and MSCs/EPCs compared to CaP-deposited NF based microsheets, as evidenced by elevated gene expression level of osteogenic and vasculogenic markers and enhanced calcium content, ALPase activity, and total collagen secretion. The osteon-mimetic scaffolds developed in this research are potentially useful as tissue engineered graft for regeneration of large bone defects.