Self-Assembly of Biomaterials for Bone Tissue Morphogenesis

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Statement of Purpose: Biomedical devices such as implants for total joint replacements, grafts to fill large bone defects and dental implants for restorative dentistry provide pain relief, restore mobility, function and are indicated for osteoarthritis and major trauma. In some cases these devices may fail causing chronic pain requiring correctional surgery. Examples of failure include post-surgical loosening of implants and stress shielding due to a modulus mismatch between the bone and graft. To attenuate incidences, we are interested in promoting direct integration of the implant with the host tissue by inducing bone growth around and into the implant using biologics and materials which mimic the bone environment. Cell regulators such as bone morphogenetic protein (BMP-2) differentiate progenitor cells into osteoblasts and induce de novo bone formation. Vascular endothelial growth factor (VEGF) causes endothelial cells to proliferate and form new blood vessels, which provide a path for these cells to migrate and is upregulated by BMP-2. Here we describe a versatile, conformal multilayer coating containing these osteophilic materials which can be applied to virtually any implant surface geometry that would mediate bone tissue morphogenesis and facilitate bonding.

Methods: Nanoscale coatings were created using a water based layer-by-layer technique, where electrostatic interactions between components of the films allowed for fine tuning of the amount of the active components. A hydrolytically degradable poly(β-amino ester) was synthesized and, along with complementary weak polyanions, used to control the presentation of growth factors on the surface of implants. Differentiation of human mesenchymal stem cells and MC3T3 pre-osteblast cells was monitored using alkaline phosphatase and alizarin red stains. A porous β-tricalcium phosphate based scaffold was coated with a combination of these factors and implanted in a muscle pocket in a rat quadriceps muscle and bone growth at this ectopic site was monitored. Coated porous implants were press fitted in a rat tibia model and the growth of trabecular bone within and around the implant was monitored with μCT and histology.

Results: Independent tuning of the release of growth factors is achievable by using a combination of multilayer coatings. Here, VEGF was presented during the early acute phase of wound healing, along with slower releasing BMP-2 for bone growth. Released VEGF and BMP-2 had an in vitro dose dependent activity on HUVEC and MC3T3 cells respectively. PCL/βTCP scaffolds coated with a combination of both these growth factors resulted in de novo bone with mineral density that was 33% higher than single growth factor BMP-2 coatings. Histology demonstrated markers for bone remodeling throughout the scaffold when VEGF eluted before BMP-2 and was restricted to the scaffold periphery when only BMP-2 was present. Next, the bone matrix

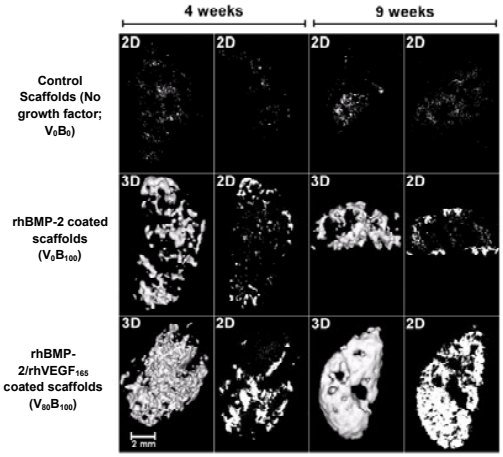

Figure 1 Scaffolds eluting no growth factors (top), only BMP-2 (middle) and VEGF and BMP-2 (bottom) at 4 and 9 weeks [5].

environment was recapitulated with films containing a combination of crystalline hydroxyapatite and BMP-2. This combination accelerated the differentiation of human mesenchymal stem cells in vitro with concurrent upregulation of osteogenic markers. Load bearing implants coated with a combination of these bone matrix materials bonded to the cortex via maturing trabecular bone, with a temporal increase in the pull-out force for all combinations of materials. Flow cytometry analysis indicated an increase in the population of MSCs expressing BMP-2 receptors, consistent with the observation of fluorescently labeled growth factor at the implant site.

Conclusions: We introduce an approach to coat implants of different geometries with osteogenic factors which results in the deposition of bone on its surface through which it can be bonded to the host bone tissue. The local availability of precise amounts of regulators is as a potent tool in tissue engineering, and can be regulated with this technique, which along with osteoconductive materials such as hydroxyapatite, results in a synergistic response which could accelerate bone regeneration and prevent premature implant failure.

References:

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