ENGINEERING AN OSTEOGENIC AND ANGIOGENIC SYNTHETIC CALCIUM PHOSPHATE CERAMIC FOR SPINAL FUSION

Yeung, HY; Lee, KM; Law, LP; Chiu, YM; Guo, X; Chow, P; Tabata, Y; Cheng, JCY
Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong, Hong Kong SAR, China

INTRODUCTION:
Spinal deformities and degenerative diseases often require surgical stabilization and posterior spinal fusion. The nonunion rate in posterior spinal fusion has been reported to range 5-35%. Having the problem in insufficient supply and quality control of autograft / allograft, researchers attempt to engineer a synthetic material that can form bone to replace the autograft / allograft. Recently, the focus is on finding an osteogenic bone substitute. However, little is done on mimicking vascularization property of autograft. Bone morphogenetic protein 4 (BMP4) is a cytokine that induce bone formation when it is implanted to muscle. Vascular endothelial growth factor (VEGF) was shown to play an important role in mediating capillary invasion and triggering endochondral ossification. In this study, we attempt to engineer an osteogenic and angiogenic bone graft by combining the cytokine and growth factor with the calcium phosphate ceramics (HA/TCP). We investigate the effect of the material in a posterior spinal fusion model [1]. This provides information on how to engineer a suitable substitute for autograft or allograft in spinal fusion surgery.

METHODS:
20 New Zealand White rabbits of 18 weeks old (about 3 kg) were divided into four experimental groups: Group 1, HA/TCP (n=6); Group 2, VEGF (10 microgram)(n=4) added HA/TCP; Group 3, BMP4 (5 microgram)(n=6) added HA/TCP; Group 4, VEGF (10 microgram) and BMP4 (5 microgram)(n=4) added HA/TCP. The calcium phosphate ceramic had the dimension of 30 x 8 x 6 mm and its composite is 60% beta-tricalcium phosphate and 40% hydroxyapatite. The pore size ranged from 250 to 500 micron. The dosage of each growth factor was chosen according to our previous studies [2,3]. Each animal underwent bilateral posterior intertransverse process spinal fusion at L5-L6 [1]. The transverse processes were not decorticated. After 7 weeks of implantation, the samples were taken from the animal and embedded in plastic without decalcification. The effect of different experimental fusion groups was evaluated by manual testing, high-resolution radiography, and histology.

ESSENTIAL RESULTS:
After 7 weeks post-operation, the implants of Group1 and Group2 can be moved slightly relative to the transverse process when manual testing is carried out. The implants of Group3 and Group4 have no relative movement to the transverse processes. When the fusion mass was studied by high-resolution radiography, the fusion gap of Group1 was 6 mm while the gap of Group2 was 1.3 mm. The gaps of Group3 and Group4 were 0.5mm and 0.6mm, respectively. The bone density of the fusion mass (BV/TV) was measured on the high-resolution radiographs (Figure 1). The bone density of Group1 is 51%. Group2 and Group3 have similar bone density of 59% and 60%, respectively. The density of Group3 (37%) is significantly lower than the other 3 groups. Histologically, Group2 and Group4 were shown to have more blood-vessel-like feature inside the ceramic implant than that of Group1 and Group3. Vascularization is enhanced in Group2 and 4. The pores of the ceramics of Group1 and Group3 were filled with fibrous-like tissue. Moreover, more new bone was formed inside the ceramics implant of Group3 and Group4. When the new bone formed in ceramics of Group3 and Group4 was compared histologically, Group4 showed a more evenly distributed new bone on the surface of the pore of the ceramics. In Group2, 3 and 4, the osteoid extensively covered the trabecular bone in the fusion mass. That may imply that the fusion mass was still undergoing activity bone formation and mineralization.

DISCUSSION:
In this study, we showed that the calcium phosphate ceramic alone could not promote fusion effectively by its own in an undecorticated spinal fusion model. The addition of either VEGF or BMP4 can enhance and provide an angiogenic and osteogenic potential to the ceramic. The BMP4 alone has been shown to greatly enhance bone formation in the present animal model. With VEGF as the second additive, the ceramics become more vascularized with better bone mineral formation in the fusion mass. The present study provides a new channel to engineer a new composite material to substitute for the conventional grafting materials. Different dosages of growth factors and combination need to be worked out in the future investigation.

Figure 1: High Resolution Radiograph

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REFERENCE:

** Department of Rehabilitation Science, The Hong Kong Polytechnic University, Hong Kong SAR, China
*** Department of Anatomy, The Chinese University of Hong Kong, Hong Kong SAR, China
**** Department of Biomaterials, Field of Tissue Engineering, Institute for Frontier Medical Sciences, Kyoto University, Japan