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Umbilical cord stem cells released from alginate–fibrin microbeads inside macroporous and biofunctionalized calcium phosphate cement for bone regeneration

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ABSTRACT

The need for bone repair has increased as the population ages. The objectives of this study were to (1) develop a novel biofunctionalized and macroporous calcium phosphate cement (CPC) containing alginate–fibrin microbeads encapsulating human umbilical cord mesenchymal stem cells (hUCMSC) and, for the first time, (2) investigate hUCMSC proliferation and osteogenic differentiation inside the CPC. A macroporous CPC was developed using calcium phosphate powder, chitosan, and a gas-foaming porogen. Five types of CPC were fabricated: a CPC control, CPC + 0.05% fibronectin (Fn), CPC + 0.1% Fn, CPC + 0.1% arginine–glycine–aspartate (RGD), and CPC + 0.1% Fn + 0.1% RGD. Alginate–fibrin microbeads containing 10^6 hUCMSC per ml were encapsulated in the CPC paste. After the CPC had set, the degradable microbeads released hUCMSC within it. The hUCMSC proliferated inside the CPC, with the cell density after 21 days being 4-fold that on day1. CPC + 0.1% RGD had the highest cell density, which was 4-fold that of the CPC control. The released cells differentiated along the osteogenic lineage and synthesized bone mineral. The hUCMSC inside the CPC + 0.1% RGD construct expressed the genes alkaline phosphatase, osteocalcin and collagen I, at twice the level of the CPC control. Mineral synthesis by hUCMSC inside the CPC + 0.1% RGD construct was 2-fold that in the CPC control. RGD and Fn incorporation in the CPC did not compromise its strength, which matched the reported strength of cancellous bone. In conclusion, degradable microbeads released hUCMSC which proliferated, differentiated and synthesized minerals inside the macroporous CPC. The CPC with RGD greatly enhanced cell function. The novel biofunctionalized and macroporous CPC–microbead–hUCMSC construct is promising for bone tissue engineering applications.

1. Introduction

Bone defects arise from skeletal diseases, congenital malformations, trauma, and tumor resection [1,2]. Millions of bone fractures occur annually in the USA [3,4]. The need for bone reconstruction is increasing as the population ages. Tissue engineering approaches are promising alternatives to autogenous bone grafts. Studies have shown exciting results on the use of scaffolds and stem cells for tissue regeneration [5–10]. Human umbilical cord mesenchymal stem cells (hUCMSC) can differentiate into adipocytes, osteoblasts, chondrocytes, neurons, endothelial cells, etc. [11–15]. The umbilical cord is an inexpensive and inexhaustible stem cell source, without the invasive procedure of bone marrow mesenchymal stem cells (MSC), and without the controversy surrounding human embryonic stem cells (hESC). hUCMSC appear to be primitive MSC with high plasticity and developmental flexibility, which did not cause immunorejection in a preliminary study and were not tumorigenic [14]. Recently several studies have examined hUCMSC for bone tissue engineering [12,15,16].

Scaffolds can serve as templates for cell attachment, differentiation and vascularization in vivo, and can then degrade and be replaced by new bone. Calcium phosphate (CaP) scaffolds mimic bone mineral and can bond to bone to form a functional interface

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