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Running title

Ectopic eingineering of osteochondral tissues in functionalized hydrogels

Abstract

Despite the various reported approaches to generate osteochondral composites by combination of different cell types and materials, engineering of templates with the capacity to autonomously and orderly develop into cartilage-bone bi-layered structures remains an open challenge. Here we hypothesized that the embedding of cells inducible to endochondral ossification (i.e. bone marrow derived mesenchymal stromal cells, BMSCs) and of cells capable of robust and stable chondrogenesis (i.e. nasal chondrocytes, NCs) adjacent to each other in bi-layered hydrogels would develop directly in vivo into osteochondral tissues. Poly(ethylene glycol) (PEG) hydrogels were functionalized with TGFß3 or BMP-2, enzymatically polymerized encapsulating human BMSCs, combined with a hydrogel layer containing human NCs and ectopically implanted in nude mice without pre-culture. The BMSC-loaded layers reproducibly underwent endochondral ossification, and generated ossicles containing bone and marrow. The NC-loaded layers formed cartilage tissues, which (under the influence of BMP-2 but not of TGFß3 from the neighbouring layer) remained phenotypically stable. The proposed strategy, resulting in orderly connected