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Mechanobiology-informed regenerative medicine: Dose-controlled release of placental growth factor from a functionalized collagen-based scaffold promotes angiogenesis and accelerates bone defect healing

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ABSTRACT

Leveraging the differential response of genes to mechanical loading may allow for the identification of novel therapeutics and we have recently established placental growth factor (PGF) as a mechanically augmented gene which promotes angiogenesis at higher doses and osteogenesis at lower doses. Herein, we sought to execute a mechanobiology-informed approach to regenerative medicine by designing a functionalized scaffold for the dose-controlled delivery of PGF which we hypothesized would be capable of promoting regeneration of critically-sized bone defects. Alginate microparticles and collagen/hydroxyapatite scaffolds were shown to be effective PGF-delivery platforms, as demonstrated by their capacity to promote angiogenesis in vitro. A PGF release profile consisting of an initial burst release to promote angiogenesis followed by a lower sustained release to promote osteogenesis was achieved by incorporating PGF-loaded microparticles into a collagen/hydroxyapatite scaffold already containing directly incorporated PGF. Although this PGF-functionalized scaffold demonstrated only a modest increase in osteogenic capacity in vitro, robust bone regeneration was observed after implantation into rat calvarial defects, indicating that the dose-dependent effect of PGF can be harnessed as an alternative to multi-drug systems for the delivery of both pro-angiogenic and pro-osteogenic cues. This mechanobiology-informed approach provides a framework for strategies aimed at identifying and evaluating novel scaffold-based systems for regenerative applications.

1. Introduction

The regeneration of large bone defects remains a significant clinical challenge [1]. The field of regenerative medicine aims to leverage the capacity of biomaterials to deliver therapeutic agents such as drugs, genes or stem cells in order to repair damaged tissues and organs [2]. One such therapeutic, which has received regulatory approval for orthopaedic procedures including lumbar spine fusion and tibial fracture repair, is recombinant human bone morphogenetic protein-2 (rhBMP-2). This therapeutic has been commercialized in the form of the INFUSE® bone graft (Medtronic), a resorbable collagen sponge soak-loaded with rhBMP-2. Following some initial clinical successes, however, a number of adverse effects were reported with the use of this drug, including infection, osteolysis, ectopic bone formation and increased cancer risk [3–7]. These damaging side-effects have been described to be the result of the uncontrolled release of supraphysiological levels of rhBMP-2 from the soak loaded collagen sponge [8]. Therefore, there has been an increased interest in the field of bone regeneration in the identification of novel, alternative therapeutics to rhBMP-2, as well as in the development of advanced three-dimensional (3D) scaffold systems for their targeted, controlled delivery.

Mechanobiology has emerged as a field at the interface of engineering and biology which investigates the influence of mechanical stimuli on multiple aspects of cell behavior including intrinsic forces,

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