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How does the pathophysiological context influence delivery of bone growth factors?☆

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ABSTRACT

"Orthobiologics" represents an important category of therapeutics for the regeneration of bone defects caused by injuries or diseases, and bone growth factors are a particularly rapidly growing sub-category. Clinical application of bone growth factors has accelerated in the last two decades with the introduction of BMPs into clinical bone repair. Optimal use of growth factor-mediated treatments heavily relies on controlled delivery, which can substantially influence the local growth factor dose, release kinetics, and biological activity. The characteristics of the surrounding environment, or "context", during delivery can dictate growth factor loading efficiency, release and biological activity. This review discusses the influence of the surrounding environment on therapeutic delivery of bone growth factors. We specifically focus on pathophysiological components, including soluble components and cells, and how they can actively influence the therapeutic delivery and perhaps efficacy of bone growth factors.

Contents

Abbreviations: AAV, adeno-associated virus; BMPs, bone morphogenetic proteins; BSA, bovine serum albumin; β-TCP, β-tricalcium phosphate; CaP, calcium phosphate; DBM, demineralized bone matrix; DCM, dichloromethane; ECM, extracellular matrix; FBGCs, foreign body giant cells; FGFs, fibroblast growth factors; GAG, glycosaminoglycan; GF, growth factor; GFR, growth factor receptors; HA, hydroxyapatite; HAC, hyaluronic acid-catechol; HepC, heparin-catechol; IGF-1, insulin like growth factor 1; IL-1, interleukin-1; IL-4, interleukin-4; MMPs, matrix metalloproteinases; M-CSF, macrophage colony-stimulating factor; mBMP, mineral binding bone morphogenetic peptide; mSBF, modified simulated body fluid; PDGFs, platelet-derived growth factors; PG, proteoglycans; PLGA, poly (lactic-co-glycolic acid); PEG, poly (ethylene glycol); PLA, poly (lactic acid); PCL, poly (ε-Caprolactone); PTH, parathyroid hormone; RANKL, receptor activator of NFκB ligand; RGD, Arginylglycylaspartic acid; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; W/O/W, water-in-oil-in-water.

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1. Introduction

Regeneration of injured or diseased bone tissue represents a tremendous clinical need. With an estimated number of over 1 million fractures each year in the United States at a cost of $10 billion; the field of bone tissue engineering is aiming at developing new technologies with the goal of meeting the clinical need [1]. Therapeutic strategies often rely on the delivery of "orthobiologics", which include bone growth factors (GFs), small molecules, pro-osteogenic cell types, and polynucleotides (e.g. RNA, DNA). As an emerging class of therapeutic agents, orthobiologics have generated a high level of interest for clinical orthopedic applications [2–4]. In this review we focus on bone growth factors, a subset of orthobiologics, as they have been widely explored in controlled release applications and have a significant recent history in clinical applications. This class of orthobiologics emerged after Urist and co-workers first demonstrated the potential of demineralized bone matrix (DBM) to induce ectopic bone formation in animal muscle pouches [5]. In subsequent studies, the investigators identified a family of bone morphogenetic proteins (BMPs), members of the transforming growth factor-β (TGF-β) superfamily, as the bone growth factors present in this matrix and responsible for inducing bone formation.

1.1. Importance of biologics delivery in orthopedic and related applications

Clinical translation of BMPs for orthopedic applications has progressed substantially over the past 30 years [2–4]. There are an extensive number of preclinical studies that have demonstrated the effectiveness of applying BMPs, and have led to the clinical introduction of rhBMP-2 and rhBMP-7 within absorbable collagen sponges for spinal fusion, open tibial fractures and oral maxillofacial applications since 2002. Specific examples include Medtronic's INFUSE® product (rhBMP-2 in collagen sponge) (Fig. 1) and Stryker's OP-1 product (rhBMP-7 in collagen sponge). Several clinical studies demonstrate the pro-osteogenic capabilities of these BMPs. For example, the use of INFUSE® in lumbar

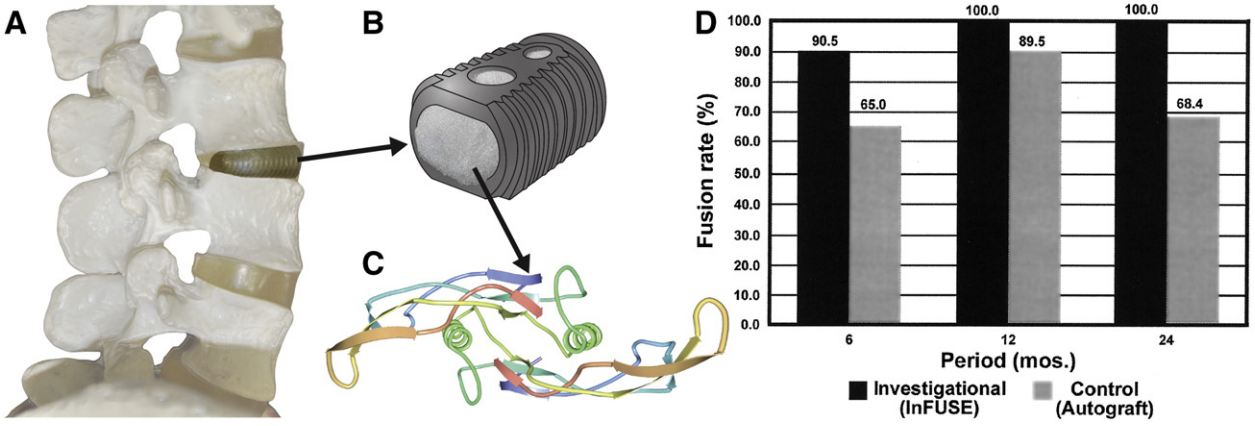

Fig. 1. Application of InFUSE™ bone grafts: A) Implantation of a lumbar interbody fusion device for spinal fusion B) a lumbar interbody tapered fusion cage representation of the InFUSE™ bone graft from Medtronic C) Crystal structure of BMP-2 (modified from www.pdb.org) D) Comparison of postoperative fusion outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft) [6]. Reproduced with permission.