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Cytokine & Growth Factor Reviews 16 (2005) 329–345
Cytokine & Growth Factor Reviews
www.elsevier.com/locate/cytogfr

Delivery of bone morphogenetic proteins for orthopedic tissue regeneration

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Available online 4 May 2005

Abstract

Carriers for bone morphogenetic proteins (BMPs) are used to increase retention of these factors at orthopedic treatment sites for a sufficient period of time to allow regenerative tissue forming cells to migrate to the area of injury and to proliferate and differentiate. Carriers can also serve as a matrix for cell infiltration while maintaining the volume in which repair tissue can form. Carriers have to be biocompatible and are often required to be bioresorbable. Carriers also have to be easily, and cost-effectively, manufactured for large-scale production, conveniently sterilized and have appropriate storage requirements and stability. All of these processes have to be approvable by regulatory agencies. The four major categories of BMP carrier materials include natural polymers, inorganic materials, synthetic polymers, composites of these materials. Autograft or allograft carriers have also used. Carrier configurations range from simple depot delivery systems to more complex systems mimicking the extracellular matrix structure and function. Bone regenerative carriers include depot delivery systems for fracture repair, three-dimensional polymer or ceramic composites for segmental repairs and spine fusion and metal or metal/ceramic composites for augmenting implant integration. Tendon/ligament regenerative carriers range from depot delivery systems to three-dimensional carriers that are either randomly oriented or linearly oriented to improve regenerative tissue alignment. Cartilage regenerative systems generally require three-dimensional matrices and often incorporate cells in addition to factors to augment the repair. Alternative BMP delivery systems include viral vectors, genetically altered cells, conjugated factors and small molecules.

Keywords: Bone morphogenetic protein; Delivery systems; Inorganic carriers; Natural polymers; Synthetic polymers; Composites; Gene therapy

1. Introduction

Accelerated closed fracture healing in rats [1], fracture healing in rabbits [2], osteotomy healing in rabbits [3] and Achilles tendon healing in rabbits [4] has been reported following treatment with bone morphogenetic proteins (BMPs) delivered in formulation buffer. However, the efficacy of formulation buffer as a delivery vehicle for BMPs to accelerate bone or tendon healing in large animal models is not as clear [5–7]. Reduced efficacy observed in large animal models using BMPs delivered in formulation buffer may be due to the combination of a reduced pool of available responsive stem cells and insufficient retention of the BMPs at the repair site to stimulate an appropriate increase in the number of responsive cells. In contrast, BMPs combined with injectable or implantable carriers with longer residence time than formulation buffer accelerate bone healing [8–27], tendon/ligament healing [28–30], and cartilage healing [31,32] in numerous studies in both small and large animal models, as well as in people. The goal of this review is to discuss the general requirements for BMP carriers, commonly used carrier materials and carrier configurations primarily for bone indications and the specific requirements for fracture repair, segmental bone repair, and implant fixation. A brief discussion of carriers for tendon/ligament and cartilage indications is also included. Alternative BMP delivery methods including viral vectors, genetically altered cells and conjugated factors will also be introduced. Several additional references discuss the use of BMP carriers in otolyrngeal [33], dental [34], craniofacial [35] and spine indications [9,36,37] that are beyond the scope of this review.

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doi:10.1016/j.cytogfr.2005.05.001

2. General requirements for BMP carriers

Carriers for BMPs are used to increase retention of these factors at orthopedic treatment sites for a sufficient period of time to allow regenerative tissue forming cells to migrate to the area of injury and to proliferate and differentiate. Carriers can also serve as a matrix for cell infiltration while maintaining a space or volume in which repair tissue formation can occur. Carriers have to be biocompatible and are often required to be bioresorbable. Carriers also have to be easily, and cost-effectively, manufactured for large-scale production, conveniently sterilized and have appropriate storage conditions and stability. All of these processes have to be approvable by regulatory agencies for the desired indication.

2.1. BMP retention at the treatment site

Several idealized scenarios are presented in Fig. 1 to illustrate the requirement for BMP carriers to increase retention of these factors at treatment sites for a sufficient period of time to allow repair tissue formation. All of the scenarios assume that there is a critical density of BMP responsive cells, and in some cases vascular support cells, required for effective orthopedic tissue formation. In addition, the scenarios assume there is a minimal concentration of exogenous BMPs required to induce these cells to generate the desired orthopedic tissue formation response. Without the presence of exogenous BMP, repair would occur at a slower rate or the segmental defect might not bridge. Once the critical density of cells is achieved, appropriate tissue formation will occur independent of any continued requirement for exogenous BMP. The scenarios also assume the same initial BMP concentration.

In the first scenario, the BMP retention profile of carrier A maintains the required minimum exogenous BMP concentration for sufficient time to allow the rapid cell population to exceed the required critical cell density to generate the desired tissue formation response. This rapid response could be due to a higher level of resident responsive cells at the repair site or a more rapid increase in the number of responsive cells. In the second scenario, the BMP retention profile of carrier A does not maintain the minimum exogenous BMP concentration for a long enough period of time to allow the slower cell population to exceed the critical cell density. The slower response may be due either to a smaller level of resident responsive cells at the repair site or a slower increase in the number of responsive cells. Once the exogenous BMP concentration falls below the minimum level, the responsive cell density either begins to fall or alternatively may remain constant. As a result, the tissue formation response is either insufficient for the desired effect or the response is aborted. In scenario 3, the increased BMP retention profile of carrier B now maintains the minimum exogenous BMP concentration for a long enough period of time to allow the slower cell population to reach the critical cell density. Given potential differences in available BMP responsive cells or differences in response rate, these scenarios help explain why certain BMP carriers are efficacious at a given BMP concentration in rodents but not in larger animals [9,18,19]. These scenarios also demonstrate the potential need for higher initial concentrations of BMPs delivered in the same carrier required in large animal models compared to rodents. Again, given the potential differences in available BMP responsive cells or differences in response rate in larger animals compared to rodents, a higher starting BMP concentration in a given BMP carrier will maintain the minimum exogenous BMP concentration for a longer period of time allowing a smaller initial cell population or slower responding cell population to reach the critical cell density for tissue formation.

A wide range of retention profiles can be achieved with various BMP/carrier combinations. Fig. 2 illustrates release profiles of rhBMP-2/carrier combinations used to treat rabbit

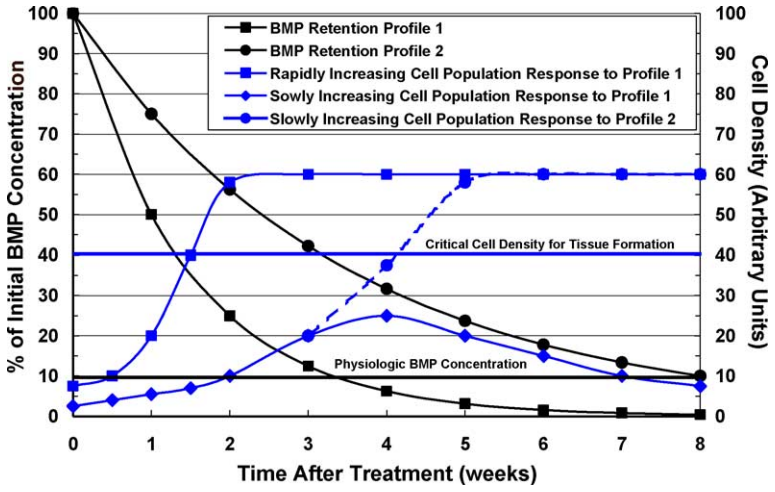

Fig. 1. Three idealized cellular responses for orthopedic repair tissues (scenarios 1–3) to two different BMP retention profiles at the site of the repair (retention profiles A and B) as a function of time after treatment (weeks).