Advanced Drug Delivery Reviews 94 (2015) 41–52

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Extracellular matrix-inspired growth factor delivery systems for bone regeneration☆

Mikaël M. Martino [a,*], Priscilla S. Briquez [b], Kenta Maruyama [a], Jeffrey A. Hubbell [b,c,d,**]

[a] Immunology Frontier Research Center, Osaka University, Osaka, Japan
[b] Institute of Bioengineering, School of Life Sciences and School of Engineering, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland
[c] Institute for Molecular Engineering, University of Chicago, Chicago, IL, USA
[d] Materials Science Division, Argonne National Laboratory, Argonne, IL, USA

ARTICLE INFO

Available online 17 April 2015

Keywords:
Controlled delivery
Bone morphogenetic protein
Vascular endothelial growth factor
Platelet-derived growth factor
Fibroblast growth factor
Extracellular matrix
Integrins
Clinical translation

ABSTRACT

Growth factors are very promising molecules to enhance bone regeneration. However, their translation to clinical use has been seriously limited, facing issues related to safety and cost-effectiveness. These problems derive from the vastly supra-physiological doses of growth factor used without optimized delivery systems. Therefore, these issues have motivated the development of new delivery systems allowing better control of the spatiotemporal release and signaling of growth factors. Because the extracellular matrix (ECM) naturally plays a fundamental role in coordinating growth factor activity *in vivo*, a number of novel delivery systems have been inspired by the growth factor regulatory function of the ECM. After introducing the role of growth factors during the bone regeneration process, this review exposes different issues that growth factor-based therapies have encountered in the clinic and highlights recent delivery approaches based on the natural interaction between growth factor and the ECM.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Drug delivery to bony tissue".

* Correspondence to: M.M. Martino, Immunology Frontier Research Center, Osaka University, 3-1 Yamadaoka, Suita, 565-0871 Osaka, Japan. Tel.: +81 668798303.
** Correspondence to: J.A. Hubbell, Institute for Molecular Engineering, University of Chicago, 5747 Ellis Avenue, Jones 222, Chicago, IL, 60637, USA. Tel.: +1 7738343548.
E-mail addresses: mmartino@ifrec.osaka-u.ac.jp (M.M. Martino), jhubbell@uchicago.edu (J.A. Hubbell).

http://dx.doi.org/10.1016/j.addr.2015.04.007
0169-409X/

1. Introduction

Unlike most tissues, bone possesses an intrinsic capacity to regenerate after injury [1,2]. The majority of bony injuries, when properly treated by re-apposition, heal without a permanent lesion, and the pre-existing properties of the bone tissue are restored through remodeling. In the clinical setting, the most common form of bone regeneration is fracture healing, during which the pathway of normal fetal skeletogenesis, including intramembranous (primary) and endochondral (secondary) ossification, is recapitulated to some extent [3]. However, there are many situations where complete bone regeneration cannot occur. For example, up to 13% of fractures occurring in the tibia are associated with delayed healing or fail to heal [4]. When a broken bone does not heal properly, it is called a "non-union", and this happens if the fracture is non-stabilized or if the bone defect is too large following a trauma or a tumor resection. Other reasons for non-union include avascular necrosis, infection, soft-tissue imposition, osteoporosis, or co-morbidities such as diabetes [5–8]. In those cases, the bone regeneration needs to be further stimulated. Standard approaches widely used in clinical practice include distraction osteogenesis, bone transport [9], and bone-grafting methods such as autologous or allogeneic bone grafts [10]. While autologous bone grafting is currently the gold standard, harvesting bone requires an additional surgical procedure, with well-documented complications and discomfort for the patient. Moreover, the quantity of bone that can be harvested is clearly limited. Therefore, extensive efforts have been made to develop bone-graft substitutes, which consist of natural or synthetic biomaterial scaffolds that promote bone regeneration. A wide range of biomaterials such as fibrin, collagen, gelatin, alginate, hydroxyapatite, β-tricalcium phosphate, and glass ceramics are currently used alone or combined [11,12]. While these biomaterials have some intrinsic osteogenic capacities, they are often not sufficient to promote complete regeneration. Indeed, optimal bone regeneration not only depends on mechanical stability and on an osteoconductive matrix, but also on osteoinductive factors and osteogenic cells [13,14]. Therefore, common strategies to promote better or faster healing consist of delivering osteoinductive growth factors and/or stem/progenitor cells through osteoconductive biomaterials.

Stem/progenitor cells are very promising to enhance bone regeneration, but showing statistically significant efficacy in clinical trials has been difficult [15,16], most likely because of stem/progenitor cell selection criteria variations and because their regenerative capability cannot readily be controlled once transplanted [15]. On the other hand, growth factors may have better capacities to promote bone regeneration [17], and several products containing recombinant growth factors have been used in orthopedic applications such as spinal fusions, non-unions, and oral surgery [18–22]. In this review, after introducing the roles of growth factors during the bone regeneration process, we will concentrate on their potential to promote bone healing and on their clinical limitations. Specifically, we will present growth factor delivery strategies inspired from the natural interaction between extracellular matrix (ECM) and growth factors.

2. Key growth factors involved in the different phases of bone regeneration

2.1. Inflammatory phase

Bone injury is typically associated with disruption of the local soft and vascular tissue integrity. This damage induces the activation of non-specific wound healing pathways that accompany non-skeletal injuries (Fig. 1A). The bleeding within the injury site develops into a hematoma, which coagulates between and around the broken bone ends forming a fibrinous clot. The first cells recruited are polymorphonuclear neutrophils, which are attracted by dead cells and debris and rapidly accumulate during the first hours after injury. Polymorphonuclear neutrophils are short-lived (around 24 hours), but secrete several chemokines such as C C motif chemokine-2 and interleukin (IL) 6 that attract longer-lived monocytes and macrophages [23]. Then, early in the inflammatory phase, degranulating platelets and macrophages release several pro-inflammatory cytokines including IL-1, IL-6, tumor necrosis factor (TNF), macrophage colony-stimulating factor (M-CSF)-1 as well as members of the transforming growth factor (TGF)-β superfamily such as bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, and BMP-6 [23,24]. At the same time, platelet-derived growth factors (PDGFs) are secreted from the alpha granules of platelets as well as from endothelial cells, vascular smooth-muscle cells, and macrophages [24].

Angiogenic factors (see below) are released as a result of the hypoxic conditions created by the disturbed vascularization. Over time, capillaries grow into the clot, which is reorganized into granulation tissue with macrophages and other phagocytic cells clearing degenerated cells and other debris [2]. The acute inflammatory response peaks within the first 24 hours and usually finishes after 7 days [25]. While the inflammation is first a protective response against potential pathogen invasion, cytokines and immune cells most likely modulate the bone regenerative process [26]. For example, TNF-α is recognized to act on both apoptotic and non-apoptotic events within mesenchymal cell types found in skeletal tissues. This includes specific types of mesenchymal precursors, osteogenic cells, and synovial fibroblasts. For instance, it has been shown that TNF-α promotes fracture repair by augmenting the recruitment and differentiation of muscle-derived stromal cells [27]. On the other hand, bone regeneration driven by bone marrow-derived mesenchymal stem cells is inhibited by TNF-α, which induces apoptosis of the stem cells [28].

2.2. Revascularization and angiogenesis

In most cases, revascularization is essential for successful bone regeneration for the obvious reason of providing nutrition and gas exchange as well as an egress for breakdown products. During intramembranous bone formation, vascularization may also provide an entrance path for osteoblast progenitors. Moreover, blood vessels are necessary for the effect of systemic circulating factors that can influence bone regeneration such as parathyroid hormone (PTH) and vitamin D [29]. In endochondral bone healing, angiogenesis not only involves angiogenic pathways, but also chondrocyte apoptosis and cartilaginous degradation as the removal of cells and extracellular matrices are necessary to allow angiogenesis within the regeneration site [1]. Pro-angiogenic factors including vascular endothelial growth factors (VEGFs), placental growth factors (PlGFs), fibroblast growth factor (FGF)-2, PDGFs, and BMPs promote angiogenesis within the soft callus (Fig. 1B) [29–34]. In addition, the angiopoietins, primarily angiopoietin-1 and -2, regulate vascular morphogenesis of larger vessels and development of collateral branches from existent vessels [24]. For example, angiopoietin-1 is expressed during the initial stages of fracture repair, suggesting that initial vascular in-growth from vessels in the periosteum plays an important role in the repair process [24].

Nevertheless, the VEGF pathway is considered to be the key regulator of vascular regeneration [35]. The VEGF family members detectable