International Immunopharmacology 16 (2013) 214–223

Contents lists available at SciVerse ScienceDirect

International Immunopharmacology

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

Review

Localized delivery of growth factors for angiogenesis and bone formation in tissue engineering

Yan Bai, Guangfu Yin *, Zhongbing Huang, Xiaoming Liao, Xianchun Chen, Yadong Yao, Ximing Pu

College of Materials Science and Engineering, Sichuan University, Chengdu 610064, P. R. China

ARTICLE INFO

Article history:
Received 10 January 2013
Received in revised form 1 April 2013
Accepted 1 April 2013
Available online 12 April 2013

Keywords:
Angiogenesis
Bone formation
Growth factors
Localized delivery

ABSTRACT

Angiogenesis is a key component of bone formation. Delivery of growth factors for both angiogenesis and osteogenesis is about to gain important potential as a future therapeutic tool. This review focuses on these growth factors that have dual functions in angiogenesis and osteogenesis, and their localized application. A major hurdle in the clinical development of growth factor therapy so far is how to assure safe and efficacious therapeutic use of such factors and avoid unwanted side effects and toxicity. It is now firmly established from the available information that the type, dose, combinations and delivery kinetics of growth factors all play a decisive role for the success of growth factor therapy. All of these parameters have to be adapted and optimized for each animal model or clinical case. In this review we discuss some important parameters associated with growth factor therapy and present an overview of selected preclinical studies, followed by a conceptual description of both established and proposed delivery strategies meeting therapeutic needs.

Contents

1. Introduction

Bone formation includes the coordination of multiple events such as activation, migration and differentiation of multiple cell types and tissues [1], which is regulated by a large number of growth factors. Biochemical stimulation of local bone healing through the delivery of growth factors can supplement conventional bone repair therapies [2–4]. However, the lack of a functional vascular supply is currently considered as the major challenge in bone tissue engineering [5–8], since the close spatial and temporal connection between blood vessels and bone cells is important to maintain skeletal integrity. Angiogenesis thus is a key point for bone development and repair. Therefore, the incidence of successful bone repair therapies could be significantly enhanced if appropriate combinations of osteogenic factors and angiogenic factors are selected and used for bone tissue engineering. Interestingly, some growth factors have dual functions, which not only regulate angiogenesis process, but also play a role in the osteogenesis process [9]. This review focuses on these growth factors that have dual functions in angiogenesis and osteogenesis, and their localized application. In this review, we describe typical difficulties related to growth factors therapy, and present an overview of selected preclinical studies, followed by a conceptual description of both established and proposed delivery strategies meeting therapeutic

* Corresponding author. Tel./fax: +86 28 85413003.
E-mail address: nic0700@scu.edu.cn (G. Yin).

1567-5769/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.intimp.2013.04.001

needs. We also describe the prime importance of customized and optimized delivery systems for successful clinical therapy. Pharmacokinetics, dose issues, synergistic effects, safety and efficacy problems are given adequate and critical attention in this review,

2. Angiogenesis and bone formation

The importance of angiogenesis during the growth and development of bone was presented as early as the 1700 s [10,11]. Bone tissue would simply degenerate and die without angiogenesis [12]. For several years, angiogenesis has remained one of the main obstacles that must be overcome to reconstruct large bone defects [13]. One of the current limitations of bone tissue engineering is the inability to provide sufficient blood supply in the initial phase after implantation. Inadequate angiogenesis after implantation leads to oxygen and nutrient limitations, which then results in cell death in the tissue-engineered constructs [14,15]. In addition, vascular network acts as a transport system for hormones, waste products, toxic and non-functional substances [16]. Vascular network is also a delivery media that releases growth factors produced locally by endothelial cells (ECs), including angiogenic factors and morphogenetic factors [17].

On the other hand, the close interaction of angiogenesis and osteogenesis was demonstrated by an intimate functional connection between ECs and osteoblasts (OBs)/osteoclasts (OCs) [18,19]. Genetic, biochemical, and pharmacological studies have identified and characterized growth factors involved in the conversation between ECs and OBs/OCs during both bone formation and repair [20,21]. Previous studies have indicated that ECs and OBs produce growth factors affecting the growth, migration and differentiation of both cell types (Fig. 1) [22,23]. Besides, the important role of OCs in the combination of calcified cartilage and newly formed woven was also affected by these growth factors [24]. Some of these growth factors are responsible for the interaction between cells of the osteoblastic and osteoclastic lineage. These growth factors are in the family of tumor necrosis factor [25]. Growth factors act via binding to their target receptors on the surface of cells and subsequently activating the intracellular signal-transduction, which ultimately results in transcription of mRNA and synthesis of the respective protein(s) [26–28]. Growth factors produced by ECs include bone morphogenetic protein-2 (BMP-2) [29], vasoconstrictor endothelin-1 (ET1) [30] and insulin-like growth factor (IGF) [31]. These growth factors affect the migration, proliferation and differentiation of OBs. OBs produce high levels of vascular endothelial growth factor (VEGF), which has been shown to regulate recruitment, survival and activity of OCs [32,33] and improve the survival time, proliferation, differentiation, angiogenesis of ECs through activating specific receptors [34–36]. OBs mediate IGF stimulation of OCs formation, recruitment and function [37] and OCs can secrete proteinases into the extracellular matrix (ECM) to stimulate OBs secreted transforming growth factor β (TGF-β) [38].

3. Growth factors

Many growth factors, expressed during blood vessels development and induced angiogenic response to injury, are believed to play a significant role in the process of bone repair [39,40]. These include members of the fibroblast growth factor (FGF), TGF, BMP, IGF, platelet derived growth factor (PDGF), VEGF, hepatocyte growth factor (HGF), erythropoietin, growth hormone, as well as parathyroid hormone (Table 1) [41–60].

VEGF has five isoforms, VEGF-A, -B, -C, -D and -E, which form homo- and heterodimers and bind to a dimeric receptor complex of their receptors [61]. VEGF is known to be a major angiogenic modulator involved in process of blood vessel formation. It stimulates ECs

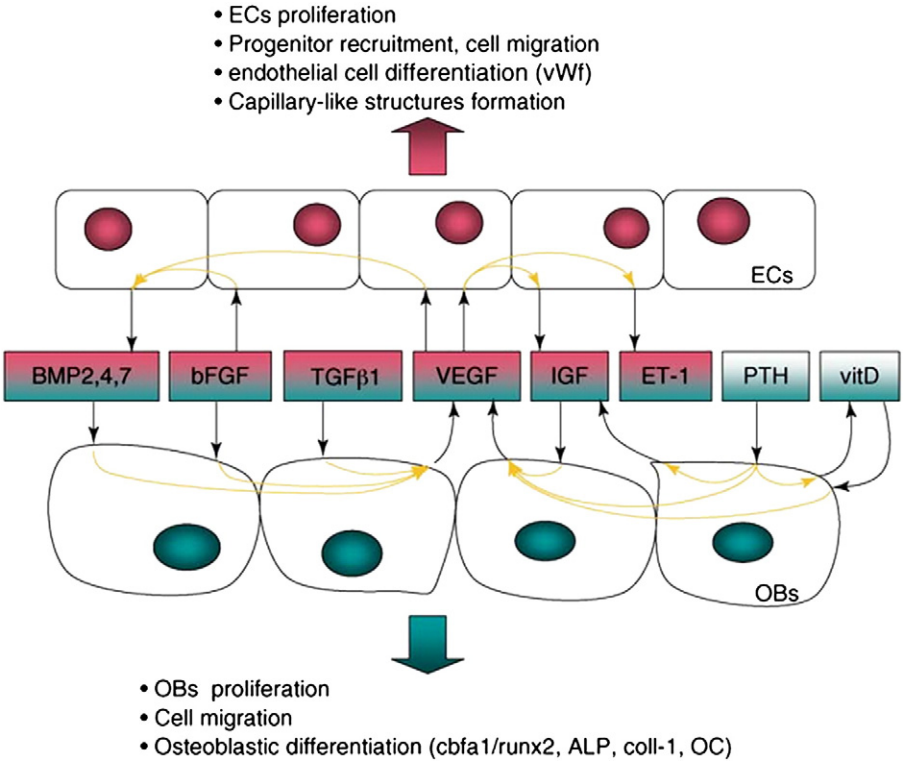

Fig. 1. Factors involved in crosstalk between osteoblastic cells and endothelial cells. Growth factors, as well as systemic hormones, can have effects on endothelial functions (red) and/or on osteoblastic functions (green). These factors act through activation of specific receptors (black arrows) that in turn stimulate the expression of other proteins after activation of intracellular signaling pathways (orange arrows). This image provides evidence that endothelial cells and osteoblastic cells can communicate with each other (from ref [23]).