Bone 80 (2015) 43–59

Contents lists available at ScienceDirect

Bone

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

Review

Bone morphogenetic protein signaling in bone homeostasis

Gonzalo Sánchez-Duffhues [a], Christian Hiepen [b,c], Petra Knaus [b,c,*], Peter ten Dijke [a,**]

[a] Department of Molecular Cell Biology and Cancer Genomics Centre Netherlands, Leiden University Medical Center, The Netherlands
[b] Institute for Chemistry and Biochemistry, Freie Universität Berlin, Berlin, Germany
[c] Berlin Brandenburg School of Regenerative Therapies (BSRT), Charité Universitätsmedizin, Berlin, Germany

ARTICLE INFO

Article history:
Received 22 December 2014
Revised 11 April 2015
Accepted 20 May 2015
Available online 5 June 2015

Keywords:
TGF-β
BMP
Bone
Osteoblast
Osteoclast

ABSTRACT

Bone morphogenetic proteins (BMPs) are cytokines belonging to the transforming growth factor-β (TGF-β) superfamily. They play multiple functions during development and tissue homeostasis, including regulation of the bone homeostasis. The BMP signaling pathway consists in a well-orchestrated manner of ligands, membrane receptors, co-receptors and intracellular mediators, that regulate the expression of genes controlling the normal functioning of the bone tissues. Interestingly, BMP signaling perturbation is associated to a variety of low and high bone mass diseases, including osteoporosis, bone fracture disorders and heterotopic ossification. Consistent with these findings, in vitro and in vivo studies have shown that BMPs have potent effects on the activity of cells regulating bone function, suggesting that manipulation of the BMP signaling pathway may be employed as a therapeutic approach to treat bone diseases. Here we review the recent advances on BMP signaling and bone homeostasis, and how this knowledge may be used towards improved diagnosis and development of novel treatment modalities. **This article is part of a Special Issue entitled "Muscle Bone Interactions".**

Contents

Abbreviations: ALK, Activin receptor-like kinase; BMP, bone morphogenetic protein; EndoMT, endothelial-to-mesenchymal transition; HO, heterotopic ossification; MAPK, mitogen activated protein kinase; MMP, matrix metalloproteinase; OB, osteoblast; OC, osteoclast; RANK, receptor activator of nuclear factor-κB (NF-κB); RANKL, receptor activator of NF-κB ligand; SMAD, homolog of the *Drosophila* protein, mothers against decapentaplegic (MAD) the *Caenorhabditis elegans* protein SMA; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α.

* Correspondence to: P. Knaus, Institute of Chemistry and Biochemistry, Freie Universität Berlin, Thielallee 63, Raum 208, 14195 Berlin, Germany.
** Correspondence to: P. ten Dijke, Dept. Molecular Cell Biology, Leiden University Medical Center, Postzone S-1-P, postbus 9600, 2300RC Leiden, The Netherlands.
E-mail addresses: Knaus@chemie.fu-berlin.de (P. Knaus), P.ten_Dijke@lumc.nl (P. ten Dijke).

http://dx.doi.org/10.1016/j.bone.2015.05.025
8756-3282/

Introduction

Bone remodeling, resorption and formation

Bone remodeling occurs throughout life and involves the coordination between bone resorption and new bone formation. Interestingly, resorption and formation are regulated by systemic and local release of cytokines and growth factors, including the bone morphogenetic proteins (BMPs). As we will describe throughout this review article, BMPs have been unveiled as crucial regulators of bone homeostasis. BMPs coordinate anabolic and catabolic processes by affecting the differentiation and activity of osteoblasts (OBs) and osteoclasts (OCs), which are the main cell types responsible for bone formation and resorption, respectively.

BMPs and other growth factors such as transforming growth factor-β (TGF-β) and insulin growth factor (IGF) are released from the digested bone matrix as well as delivered from OC-like cells to activate osteogenesis, which is initiated with the recruitment of mesenchymal OB precursors. Next, differentiated chondrocytes and active OBs generate the organic bone matrix that will be further maturated with the incorporation of inorganic salts. Finally, mature OBs embedded in the mineralized bone undergo apoptosis or differentiate into quiescent osteocytes [1]. Such anabolic and catabolic activities are coupled through *basic multicellular units* (BMU) (Fig. 1), which resemble anatomical microenvironments where bone remodeling takes place. It consists of OBs and OCs, but also osteocytes, bone lining cells and capillaries [2]. This whole multicellular assembly moves in three dimensions throughout the bone matrix to rebuild the bone architecture. Interestingly, the cells in the BMU are not directly in contact with the bone marrow, but covered by a *canopy* of bone lining/OB-like cells intimately associated with capillaries, comprising the *bone remodeling compartment* (BRC). This structure is thought to be of crucial importance since it facilitates the release of certain molecules (such as thyroid hormone, estrogen, vitamin D, parathyroid hormone and circulating BMPs) from the blood vessels [3]. Interestingly, disruption of the *canopy* leads to disorders in bone homeostasis [4], partially due to a decrease in the recruitment and differentiation of OCs and OBs.

Bone remodeling requires the formation of new blood vessels or *angiogenesis*, which provides the bone remodeling site with osteogenic precursors, as well as cytokines and growth factors that regulate the activity of OBs and OCs [5–9]. Capillaries also facilitate the diffusion of the growth factors and minerals delivered from the degraded bone matrix [10] to the peripheral blood. In fact, disruption in angiogenesis usually leads to defects in bone remodeling and repair [11]. Noteworthy, OBs, osteocytes and OCs secrete molecules such as vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) to modulate the angiogenic response [3], suggesting that there is a bilateral communication between blood vessels and bone tissues to regulate each other. Finally, although not directly involved in bone remodeling, the bone tissue is continuously invaded by immune cells, that modulate the activity

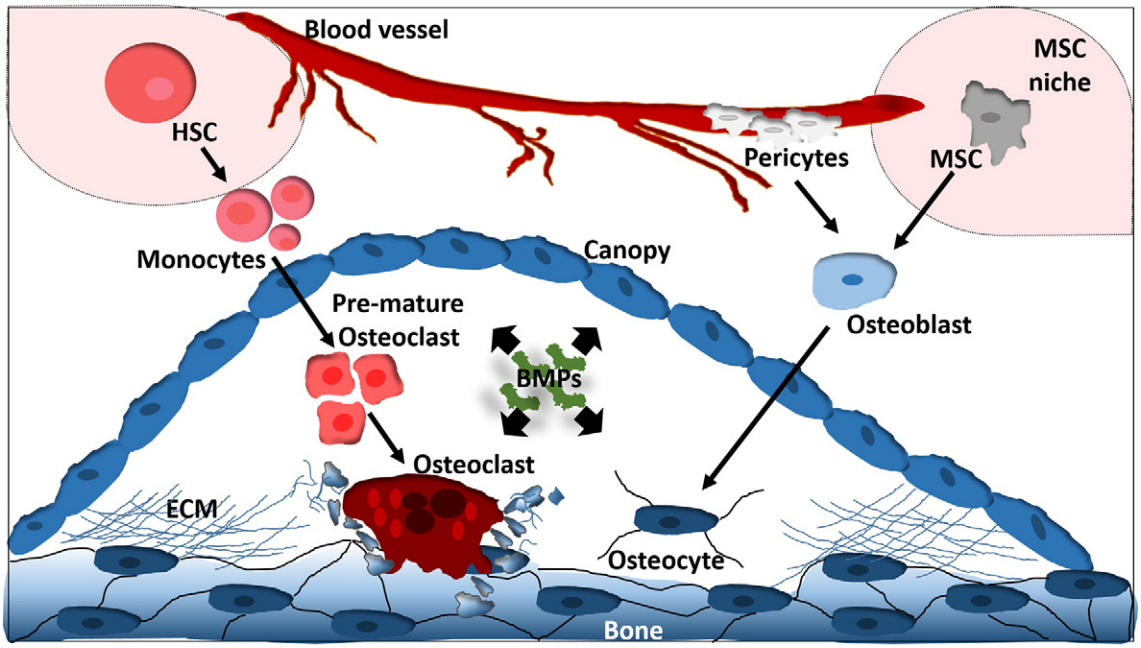

Fig. 1. Basic multicellular units (BMU). BMU represent functional bone remodeling entities where the main cell types involved in bone remodeling (i.e., mesenchymal progenitors that will differentiate into osteoblasts and osteocytes, osteoclasts and osteoclast progenitors and blood vessels consisting of endothelial cells and pericytes) are represented. A canopy made of mesenchymal cells (in humans) or osteomacs (in mice) facilitates the interchange of molecules between the bone tissue and the vasculature. HSC, hematopoeitic stem cell; ECM, extra-cellular matrix; MSC, mesenchymal stem cell.