The International Journal of Biochemistry & Cell Biology 79 (2016) 14–23

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

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

Review article

Cell-specific paracrine actions of IL-6 family cytokines from bone, marrow and muscle that control bone formation and resorption

Natalie A. Sims [a,b,*]

[a] St. Vincent's Institute of Medical Research, Fitzroy, Victoria, Australia
[b] University of Melbourne, Department of Medicine at St. Vincent's Hospital, Fitzroy, Victoria, Australia

ARTICLE INFO

Article history:
Received 8 April 2016
Received in revised form 1 August 2016
Accepted 3 August 2016
Available online 3 August 2016

Keywords:
Gp130
Il6st
Osteoblast
Osteoclast
Osteocyte

ABSTRACT

Bone renews itself and changes shape throughout life to account for the changing needs of the body; this requires co-ordinated activities of bone resorbing cells (osteoclasts), bone forming cells (osteoblasts) and bone's internal cellular network (osteocytes). This review focuses on paracrine signaling by the IL-6 family of cytokines between bone cells, bone marrow, and skeletal muscle in normal physiology and in pathological states where their levels may be locally or systemically elevated. These functions include the support of osteoclast formation by osteoblast lineage cells in response to interleukin 6 (IL-6), interleukin 11 (IL-11), oncostatin M (OSM) and cardiotrophin 1 (CT-1). In addition it will discuss how bone-resorbing osteoclasts promote osteoblast activity by secreting CT-1, which acts as a "coupling factor" on osteocytes, osteoblasts, and their precursors to promote bone formation. OSM, produced by osteoblast lineage cells and macrophages, stimulates bone formation via osteocytes. IL-6 family cytokines also mediate actions of other bone formation stimuli like parathyroid hormone (PTH) and mechanical loading. CT-1, OSM and LIF suppress marrow adipogenesis by shifting commitment of pluripotent precursors towards osteoblast differentiation. Ciliary neurotrophic factor (CNTF) is released as a myokine from skeletal muscle and suppresses osteoblast differentiation and bone formation on the periosteum (outer bone surface in apposition to muscle). Finally, IL-6 acts directly on marrow-derived osteoclasts to stimulate release of "osteotransmitters" that act through the cortical osteocyte network to stimulate bone formation on the periosteum. Each will be discussed as illustrations of how the extended family of IL-6 cytokines acts within the skeleton in physiology and may be altered in pathological conditions or by targeted therapies.

Contents

Abbreviations: C/EBPβ, CCAAT enhancer binding protein-beta; C/EBPδ, CCAAT enhancer binding protein-delta; CNTF, ciliary neurotrophic factor; CNTFR, ciliary neurotrophic factor receptor; CLCF1, cardiotrophin-like cytokine factor 1; CRLF1, cytokine receptor-like factor 1; CT-1, cardiotrophin 1; ΔFosB, truncated FBJ murine osteosarcoma viral oncogene homolog B; Erk, extracellular signal-related kinase; gp130, glycoprotein 130 (also known as IL-6 signal transducer); IL-6, Interleukin 6; IL-6, RInterleukin 6 receptor; IL-11, Interleukin 11; IL-11, RInterleukin 11 receptor; IL-27Rα/WSX-1, Interleukin 27 receptor; JAK/STAT, Janus kinase/signal transducer and activator of transcription; LIF, leukemia inhibitory factor; LIFR, leukemia inhibitory factor receptor; M-CSF, macrophage colony stimulating factor; OSM, oncostatin M; OSMR, oncostatin M receptor; PKCδ, Protein Kinase C δ; PTH, parathyroid hormone; RANKL, receptor activator of NFkappaB ligand; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

* Corresponding author.
E-mail address: nsims@svi.edu.au

http://dx.doi.org/10.1016/j.biocel.2016.08.003
1357-2725/

1. Introduction

Bone structure is determined and maintained by co-ordinated activities of two key cell types: osteoblasts (bone forming cells), and osteoblasts (bone resorbing cells). In the adult, once the size and shape of the skeleton is established, bone tissue is continually renewed and adapted to physiological stresses by a process termed remodelling. In this process, the amount of bone removed by the osteoclast must be matched to that formed by the osteoblast for bone structure and strength to be maintained. In osteoporosis, including secondary osteoporosis associated with inflammatory conditions where cytokine levels are elevated, the activity of osteoclasts outstrips that of osteoblasts, leading to bone loss; similar mechanisms exist at sites of local inflammation and local bone destruction, for example in rheumatoid arthritis.

It was through the study of bone-resorbing osteoclasts that a role of Interleukin 6 (IL-6) family cytokines in the skeleton was first discovered (Tamura et al., 1993). Indeed IL-6 was one of the first factors identified that stimulates osteoclast formation not by directly stimulating haematopoietic osteoclast precursors, but by promoting the ability of mesenchymal osteoblast lineage cells to support osteoclastogenesis in a contact-dependent manner. This RANKL-dependent communication pathway that intimately links osteoblasts to osteoclasts is now central to our understanding of the way that skeletal structure is controlled and an established mechanism by which osteoporosis is treated (Ominsky et al., 2011).

In recent years it has become clear that IL-6 and its related family of cytokines have multiple roles that regulate not only bone resorption, but also bone formation in health and disease, by virtue of their expression in normal physiology, and their elevated levels in pathologies. This review will describe a number of key intercellular pathways through which cell-specific production of IL-6 family cytokines regulate skeletal structure with a focus on the roles identified in studies of genetically altered mice.

2. The IL-6 family

The IL-6 family of cytokines is defined by their common use of the glycoprotein 130 (gp130) co-receptor, a ubiquitously expressed transmembrane receptor subunit capable of intracellular signalling. The most widely studied members of the family are IL-6, interleukin 11 (IL-11), leukemia inhibitory factor (LIF), cardiotrophin-1 (CT-1), oncostatin M (OSM) and ciliary neurotrophic factor (CNTF). Each cytokine that binds to gp130 generates specific intracellular JAK/STAT or Erk signalling cascades by forming specific receptor:ligand complexes, each with distinct components (Fig. 1).

A subfamily of compound cytokines that form overlapping signalling complexes including the CNTF receptor also exists; their specific roles in the skeleton appear to be limited to promoting bone formation, but remain very poorly understood and largely unexplored despite known skeletal defects in patients with mutations in these family members (Knappskog et al., 2003; Rousseau et al., 2006). This has been recently reviewed (Sims, 2015), and will not be discussed in detail here. Another series of cytokines that act through gp130-containing complexes are those that utilize IL-27Rα/WSX-1 (Interleukin 27 receptor). There is very little known about these cytokines in bone, even though IL-27Rα has been detected in human osteoblasts, at least in the context of multiple myeloma (Cocco et al., 2010). IL-27 suppresses inflammation in a preclinical model of rheumatoid arthritis (Niedbala et al., 2008) and suppresses the pathway by which T cells support osteoclast formation (Kamiya et al., 2011). No report of effects of humanin on osteoblasts or osteoclasts has been made. For this reason IL-27Rα-signalling cytokines will not be discussed in this review.

3. Intercellular communication in bone growth and remodelling

During bone growth, shape change results from bone being deposited on surfaces where it is needed and removed from areas where it is no longer needed; in this process, termed “bone modelling”, osteoblasts and osteoclasts act on different bone surfaces (Fig. 2). Even though they are separated by both time and place, there appears to be some co-ordination between these processes, possibly by factors recently termed “osteotransmitters” (Johnson et al., 2015) or by changing mechanical needs sensed by osteocytes (Schaffler et al., 2014) a population of mature osteoblast lineage cells residing within the bone matrix that form an extensive network throughout the skeleton (Buenzli and Sims, 2015) (Fig. 2).

Bone size is also determined by other cells not classically considered “bone cells”. Proliferation and differentiation of chondrocytes within cartilaginous growth plates determines bone length (Fig. 2) (Sims et al., 2000), and cytokines released by muscle adjacent to cortical bone may also control the widening of cortical bone (Johnson et al., 2014b). IL-6 family members have been implicated in both of these processes (see below).

In adult life, the skeleton is renewed through a process termed bone remodelling (Fig. 2). During bone remodelling, small packets of bone are removed by osteoclasts and replaced by osteoblasts. In contrast to modelling, the process of remodelling involves osteoblasts and osteoclasts acting on the same surface but at different times. The activity of osteoblasts follows that of osteoclasts in a process termed “coupling”; factors produced by the osteoclast, termed “coupling factors” were proposed to mediate this (Martin and Rodan, 2001; Martin and Sims, 2005), and many have now been identified (Martin, 2014; Sims et al., 2015), and see below. This interaction between osteoblasts and osteoclasts does not occur in isolation, however. Other cells within the bone microenvironment, such as macrophages, T cells, and the vasculature also provide signals that control bone remodelling (Sims and Martin, 2014).

In addition to the signals from osteoclasts that control bone formation, communication also occurs in the opposite direction, where cells of the osteoblast lineage, including osteoblast precursors and the matrix-embedded osteocyte, support the formation of osteoclasts by their production of RANKL (receptor activator of NFκB ligand) and M-CSF (macrophage colony stimulating factor), two factors required for the differentiation of osteoclasts (Kong et al., 1999; Rodan and Martin, 1981; Xiong et al., 2011). It was through the study of this pathway that the role of IL-6 family cytokines in the skeleton first reached prominence.

4. The roles of IL-6 family members in promoting bone resorption

All IL-6 family cytokines, apart from the CNTFR-binding subfamily, stimulate osteoclast formation in cell culture, through an action that requires the presence of osteoblasts (McGregor et al., 2010; Richards et al., 2000; Tamura et al., 1993; Udagawa et al.,