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Review

Regulation of cortical and trabecular bone mass by communication between osteoblasts, osteocytes and osteoclasts

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ABSTRACT

The size and strength of bone is determined by two fundamental processes. One process, bone remodelling, renews the skeleton throughout life. In this process existing bone is resorbed by osteoclasts and replaced, in the same location, by osteoblasts. The other process is bone modelling, where bone formation and resorption occur at different sites so that the shape of bone is changed. Recent data suggests that both remodelling and modelling are controlled by signals between the cells that carry out these two processes. Osteoclasts both resorb bone, and provide inhibitory and stimulatory signals, including cardiotrophin-1 and sphingosine-1-kinase, to the osteoblast lineage thereby regulating their differentiation and activity on both trabecular and cortical surfaces. In addition, the osteoblast lineage, including osteoblast progenitors, matrix-producing osteoblasts, bone lining cells, and matrix-embedded osteocytes, produce both inhibitory and stimulatory factors that stimulate osteoclast differentiation. We will discuss the roles of osteoblast- and osteocyte-derived RANKL, and paracrine, autocrine and endocrine factors, such as ephrinB2, the IL-6/gp130 family of cytokines, parathyroid hormone, and its related peptide, PTHrP. These factors not only stimulate RANKL production, but also stimulate osteoblast differentiation and activity. This review will focus on recent data, generated from pharmacological and genetic studies of mouse models and what these data reveal about these pathways at different stages of osteoblast differentiation and their impact on both bone remodelling and modelling in trabecular and cortical bone.

Introduction

The skeleton is constantly remodelled by repeated cycles of cellular activity occurring asynchronously throughout the skeleton in which tiny packets of bone are resorbed and then replaced. This process always occurs in the same sequence: bone resorption by osteoclasts followed by bone matrix production by osteoblasts. This is the fundamental process by which the skeleton changes in response to hormonal and mechanically-induced stresses.

In addition to this process, bone also adapts by the process of modelling; here bone formation and resorption do not occur in sequence at the same site. Modelling occurs during growth, and in response to mechanical loading; it can also be induced by pharmacological agents that promote bone formation without a requirement for prior resorption [1]. Modelling is also responsible for cortical expansion, where osteoblasts on the periosteal surface continue to form bone at the diaphysis of the long bones (Fig. 1). The mechanisms that determine why some bone surfaces remodel while others model are not known, but understanding the relationships between the cells involved in modelling and remodelling holds great potential for developing therapeutics that can restore bone strength in osteoporosis.

Originally, the basic multicellular unit (BMU)[1] responsible for remodelling was thought to consist of two classes of specialized cells on the bone surface, osteoclasts and osteoblasts, which contribute to remodelling by bone resorption and formation, respectively. Although osteoclasts are derived from the hemopoietic lineage, and osteoblasts from the mesenchymal lineage, these cell types act in close apposition and regulate the function of the other lineage by appropriate production of both inhibitory and stimulatory factors [2,3]. Over the past 50 years, this concept has been refined, and a

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[1] *Abbreviations used:* BMU, basic multicellular unit; RANKL, Receptor Activator of NFκB Ligand; OPG, osteoprotegerin; PTH, parathyroid hormone; BMD, bone mineral density; CTHRC1, collagen triple helix repeat containing 1; CT-1, Cardiotrophin-1; VDR, vitamin D receptor; PTHR1, PTH receptor; LIF, leukemia inhibitory factor; OSM, oncostatin M; CNTF, ciliary neurotrophic factor.

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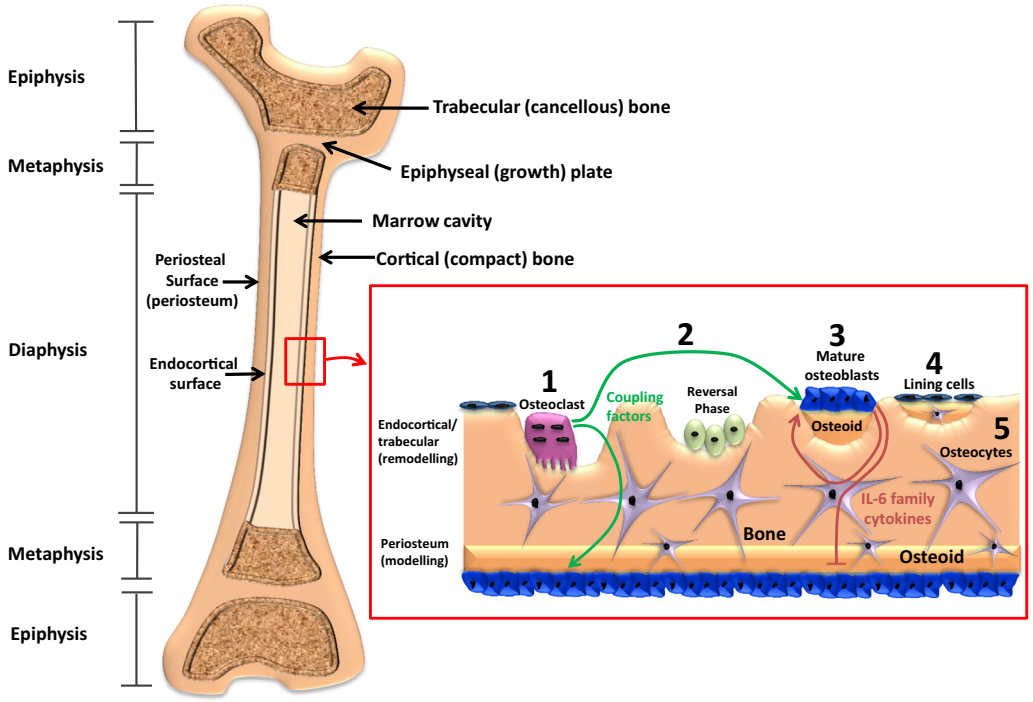

Fig. 1. Structure of trabecular and cortical bone, the process of bone remodelling, and cellular signals from coupling factors and the IL-6 cytokine family that regulate bone remodelling and periosteal modelling. The proximal and distal ends of the growing murine femur (epiphyses) contain a high proportion of trabecular (cancellous) bone. Trabecular bone is also prevalent in the metaphyses, which is separated from the epiphysis by the epiphyseal (growth) plate; this is the site of longitudinal bone growth. The midshaft of the femur, diaphysis, contains a high proportion of cortical (compact) bone that surrounds the inner marrow space and trabecular regions. Bone remodelling occurs on trabecular surfaces, and on the endocortical surface (both surfaces together are termed the endosteum). Bone modelling occurs throughout life in murine bones on the outer periosteal surface (periosteum). During bone remodelling on the endosteum, (1) osteoclasts attach to the bone surface, resorb bone and release coupling factors that stimulate osteoblast differentiation on the endosteal surface. These coupling factors also signal to periosteal osteoblasts, perhaps through the osteocyte canalicular network. After the reversal phase, which remains poorly understood in murine bones, (2) pre-osteoblasts mature, attach to the bone surface and fill the cavity created by osteoclasts with bone matrix, termed osteoid. (3) Mature osteoblasts, when their task of producing osteoid is completed, become lining cells or (4) become embedded within the osteoid as it is mineralised. These osteoblasts become osteocytes and release factors that regulate mineralisation. IL-6 family cytokines are released by the osteoblast lineage and act to stimulate osteoblast differentiation and bone matrix production on endosteal surfaces, but limit osteoblast activity on the periosteum.

number of regulatory factors have been identified, some of which we discuss below [4–7]. The best understood example of this intercellular regulation is the production of both the osteoclast stimulus Receptor Activator of NFκB Ligand (RANKL) and its decoy receptor inhibitor osteoprotegerin (OPG) by cells of the osteoblast lineage [8]. It is therefore, the same cell lineage that both forms bone matrix and regulates osteoclast differentiation in response to paracrine and endocrine stimuli, including parathyroid hormone (PTH), 1,25-dihydroxyvitamin-D_3 and cytokines [9–11]. The osteoblast lineage includes committed osteoblast precursors, matrix-producing osteoblasts, lining cells and matrix-embedded osteocytes; the major contributing cells to these two activities are unlikely to be at the same stage of differentiation within the lineage, and this concept is discussed below. Similarly, osteoclasts produce a range of "coupling factors". This is achieved both by releasing factors from the bone matrix itself during the process of resorption, and by production of soluble, and possibly membrane bound, regulators of bone formation (for recent reviews see [4,7,12]).

Although the initial concept of remodelling focussed on the cells on the bone surface, we now understand that there are many other cellular contributors that regulate bone formation and resorption within the BMU. These include osteocytes, terminally differentiated osteoblast lineage cells that reside in an interconnected network that extends throughout the bone matrix, and multiple cell types in the marrow space (e.g., haemopoietic precursors, macrophages, T-cells, natural killer cells and adipocytes) [13]. Furthermore, different stages of osteoblast differentiation are now understood to play distinct roles in regulating the activities of osteoclasts [13], and each other [14]. This is particularly relevant for the initiation of the bone remodelling cycle, where osteocytes and osteoprogenitors produce the RANKL required for osteoclastogenesis [7].

The identification of a bone remodelling canopy that lifts from the bone surface when osteoclastic resorption initiates the remodelling cycle to enclose the BMU in an isolated environment is a concept that has been explored at length in human specimens by the Delaissé laboratory [15,16]. This would provide a controlled locale in which osteoblast lineage cells, osteoclasts, and potentially other contributing marrow cells, may exchange factors and influence precursors provided by the associated vasculature. However, experimental interrogation of its contribution to the actions of specific coupling factors using genetically altered mouse models is limited because this anatomical structure has not been observed in the mouse, the model that has been used most extensively for defining the intercellular signalling pathways that modify bone remodelling.

Much work using genetically altered mice has focussed on the overall influence of these pathways on the internal trabecular network (Fig. 1), including the quantity of trabecular bone and the level of trabecular remodelling. However, major questions remain about the effects of the intercellular signalling pathways that regulate the cortical bone (Fig. 1), and cortical bone matrix quality and strength. Since it is now understood that intra-cortical remodelling and cortical bone loss are contributors to skeletal fragility [1], more attention is beginning to be paid to differences in effect of signalling pathways in cortical vs. trabecular bone. This review will focus on some notable intercellular pathways that control bone mass and bone strength in cortical and trabecular bone, as examples of