ABSTRACT. Osteoblasts and osteoclasts are derived from progenitors originating in the bone marrow, and the process of bone remodeling is controlled by growth factors and cytokines which regulate the birth and death of these cells. An overproduction of osteoclasts relative to the need for remodeling, and an undersupply of osteoblasts relative to the need for cavity repair, represent the fundamental pathophysiologic changes in postmenopausal and age-related osteopenia, respectively. As in these two forms of the disease, the osteoporosis induced by glucocorticoid excess is also caused by changes in the birth and death of bone cells, and in particular a decrease in osteoblastogenesis in the bone marrow, and an increased rate of osteoblast and osteocyte apoptosis. 

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INTRODUCTION

Regeneration, a process common to several tissues, occurs throughout life in bone as well. During development and growth, the skeleton is sculpted in order to achieve its shape and size by the removal of bone from one site, and deposition at a different one; this process is called modeling. Once the skeleton has reached maturity, regeneration continues in the form of a periodic replacement of old bone with new at the same location. This process is called remodeling, and is carried out by teams of juxtaposed osteoclasts and osteoblasts, termed basic multicellular units (BMU) (1).

Both osteoblasts and osteoclasts are derived from precursors originating in the bone marrow: osteoblasts from multipotent mesenchymal stem cells, and osteoclasts from hematopoietic progenitors, most likely the colony forming units for granulocytes-macrophages (CFU-GM) (2, 3). The development of osteoclasts from their hematopoietic progenitors, and of bone forming osteoblasts from mesenchymal stem cells is controlled by a large network of growth factors and cytokines produced in the bone microenvironment, as well as by systemic hormones (4), and molecules that mediate cell-cell and cell-matrix interactions (5). Although many details remain to be established about the operation of this network, a few themes have emerged. First, several of the growth factors and cytokines control each other’s production in a cascade fashion, and in some instances form negative feedback loops. Second, there is extensive functional redundancy among them. Third, some of the same factors are capable of influencing the differentiation of both osteoblasts and osteoclasts. Fourth, agents arising from the circulation (i.e., endocrine hormones) influence the process of osteoclast and osteoblast formation by controlling the production and/or action of the local mediators.

A disturbance of bone remodeling underlies most metabolic bone diseases, including osteoporosis. Specifically, the hallmark of osteoporosis is a reduction of skeletal mass caused by an imbalance of bone resorption over bone formation. Loss of gonadal function, aging and glucocorticoid excess are some of the most common contributing factors to the development of this disease. In this article, I will review current ideas about the bone remodeling process and the pathophysiology of these three forms of osteoporosis.

Key words: Aging, bone marrow, cytokines, glucocorticoids, postmenopausal osteoporosis.
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CURRENT CONCEPTS OF BONE REMODELING

During life, the skeleton requires periodic replacement of old bone by new (1, 6). This process proceeds in highly regulated cycles, in which osteoclasts adhere to bone, and subsequently remove it by acidification and proteolytic digestion. After osteoclasts have left the resorption site, osteoblasts invade the area and begin the process of new bone formation by secreting osteoid, which is eventually mineralized into new bone. Adult bone remodeling is responsible for the complete renewal of the skeleton every ten years. Remodeling takes place mainly on the internal surfaces of bone and, as mentioned above, is carried out by a team of juxtaposed osteoclasts and osteoblasts, comprising the basic multi-cellular unit (BMU). The BMU has an average life span of six months. In cortical bone, the BMU tunnels through the tissue, while in cancellous bone, it moves across the trabecular surface forming a trench. In both situations, the cellular components of BMU maintain a well orchestrated spatial and temporal relationship with each other. The purpose of remodeling is not entirely clear, although in bones that are load bearing, remodeling most probably serves to repair fatigue damage and prevent excessive aging and its consequenc- es.

Ideas developed to explain the coordinate regulation of bone resorption and formation center on the notion that osteogenic growth factors are released from the bone matrix during bone resorption, and mediate the subsequent recruitment of osteoblasts to the remodeling site (7, 8). Nonetheless, the life history of the BMU comprises separate stages of origination, progression, and termination, of which the second is by far the longest. As the cells that constitute the BMU advance during the progression phase, the same spatial relationships between the cells are maintained, and thus new cells are needed simultaneously to sustain the continued advance of the BMU. At first, the simultaneous need for osteoclasts and osteoblasts during the progression phase of the BMU, and thereby the simultaneous development of both osteoclast and osteoblast progenitors, is inconsistent with the sequential appearance of osteoclasts followed by osteoblasts at the same remodeling site. This paradox can be resolved by recent work from our group as well as others indicating that mesenchymal cell differentiation toward the osteoblast phenotype, and osteoclastogenesis are inseparably linked, as both are stimulated by the same factors, proceed simultaneously, and osteoclastogenesis cannot occur without mesenchymal cell differentiation to the osteoblastic lineage (9-12). Based on these considerations, we have proposed an alternative, and most likely complementary, mechanism whereby bone formation and resorption are orchestrated through the coordinated regulation of osteoclastogenesis and osteoblastogenesis in a parallel, as compared to a sequential, fashion (4).

During bone remodeling and the movement of the BMU across the bone surface, osteoblast and osteoclast precursors are exposed to paracrine signals delivered from other microenvironmental cells, autocrine signals generated by the timely expression of various growth factor genes and/or their receptors, chemotactic and adhesion molecules present in the bone surfaces, as well as systemic signals derived from the circulation (i.e., hormones). Fine orchestration of all these signals must occur to ensure that the proper number of mature osteoblasts and osteoclasts are produced to meet the needs of the bone regeneration process, and that the correct number of each cell type arrives at the remodeling site at the proper time. Even though all the details of such orchestration are far from clear, there is now compelling evidence that the orderly birth of osteoclasts and osteoblasts from their respective progenitors in the bone marrow, and the incidence of their apoptosis are essential determinants of the number of either cell type in the BMU, and thereby critical for the maintenance of bone homeostasis (13). This contention is strongly supported by the recent elucidation of the mechanism of several forms of osteoporosis.

THE PATHOPHYSIOLOGY OF THE OSTEOPOROSIS ASSOCIATED WITH SEX STEROID DEFICIENCY

At menopause (or after castration in men), the rate of bone loss in the spine increases by as much as tenfold. These clinical observations can be now explained by evidence that sex steroids exert bone protective effects, at least in part, by regulating the development of bone cells in the marrow, as well as the rate of death of mature cells (apoptosis), via their ability to alter the production of cytokines, and probably the responsiveness of bone marrow cell progenitors to cytokines.

The IL-6 story

The best documented paradigm of a cytokine playing a critical pathogenetic role in the osteoporosis caused by loss of sex steroids is interleukin-6 (IL-6). Indeed, the production of IL-6 by cells of the stromal/osteoblastic lineage is inhibited in vitro by estrogen, selective estrogen receptor modulators (SERMs), such as raloxifene, and androgen, through receptor-medi-