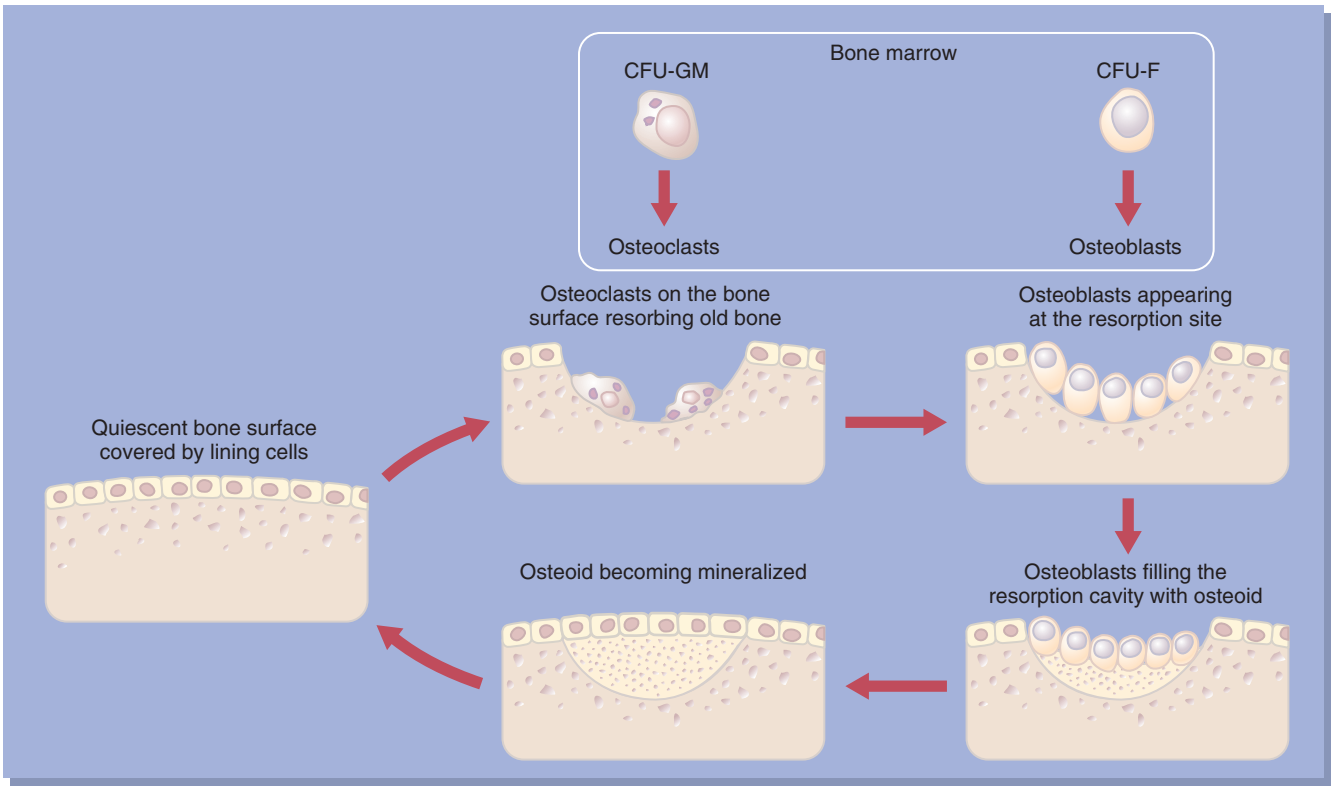


**FIGURE 72-3** Cellular components of bone remodeling. Bone remodeling is a continuous process that involves the activation of osteoclast precursors in the macrophage lineage (i.e., colony-forming units of granulocyte-macrophage progenitors [CFU-GM]) that become actively resorbing osteoclasts, which tunnel into the bone surface to dig resorption lacunae. Osteoblast precursors in the fibroblast–bone marrow stromal cell lineage (CFU-F) then appear and become active at the sites of prior resorption, and they secrete new osteoid, which later mineralizes to fill the lacunae created by osteoclastic bone resorption. (From Manolagas SC, Jilka RL: Bone marrow, cytokines, and bone remodeling: emerging insights into the pathophysiology of osteoporosis, N Engl J Med 332:305–311, 1995.)

deoxypyridinoline cross-links (i.e., collagen fragments and hydroxyproline), can be used clinically as indices of bone resorption.

New bone formation is accomplished by *osteoblasts,* which are derived from marrow stromal cells or bone surface lining cells. Osteoblasts synthesize and secrete the components of the nonmineral phase of bone, called *osteoid.* The components are mostly proteins and include collagen, osteopontin, osteonectin, osteocalcin, proteoglycans, and a plethora of growth factors, including transforming growth factor-β and insulin-like growth factor-I. This complex provides the scaffolding on which the mineral crystal hydroxyapatite forms lattices.

In the past decade, attention has focused on a third, previously underappreciated bone cell type, the *osteocyte.* These cells are descendants of osteoblasts and are embedded into the mineralized phase of bone. Osteocytes physically connect with one another and to cells at the mineral surface through long dendritic processes. The dendritic processes extensively permeate the mineralized phase of bone through an elaborate canalicular network. Osteocytes serve a critical role in sensing biomechanical strain within bone, and through their cellular extensions to the cell surface, they communicate signals that attract, activate, or repress osteoclasts and osteoblasts. In this way, they determine which areas of the skeleton require new bone formation and which need to be targets of osteoclastic bone remodeling.

Through the process of bone turnover, or bone remodeling, osteoclasts continually remove old bone, and osteoblasts continually produce new osteoid that mineralizes, eventually replacing the old bone removed by osteoclasts with new bone. This process replaces old bone—and by implication, defective or damaged bone with microfractures and reduced mechanical strength—with new, mechanically strong bone, although the evidence for this action is limited. The principal therapy for osteoporosis is with the use of antiresorptives such as estrogens, estrogen-like drugs, and bisphosphonates, which dramatically reduce bone turnover while improving bone mass and bone mechanical properties.

Bone remodeling is important for systemic calcium homeostasis. Osteoclasts can be used to access calcium from the skeleton in times of need to maintain a normal serum calcium concentration. Conversely, unmineralized osteoid produced by osteoblasts can be used at appropriate times as a sink into which excess serum calcium can be deposited. Under normal circumstances, osteoclasts resorb bone at a rate such that about 500 mg of calcium is removed per day from the skeleton and delivered to the ECF compartment. At the same time, osteoblasts produce osteoid that mineralizes at a rate such that about 500 mg of calcium leaves the ECF and enters the skeleton at new sites. From the perspective of the black box shown in Figure 72-1, the skeleton is in zero calcium balance with the ECF, and the whole organism is in zero calcium balance with the external environment.

Considering the complexity of this calcium homeostatic system and the importance of maintaining tight control of serum calcium levels, an obvious need exists for systemic regulation and