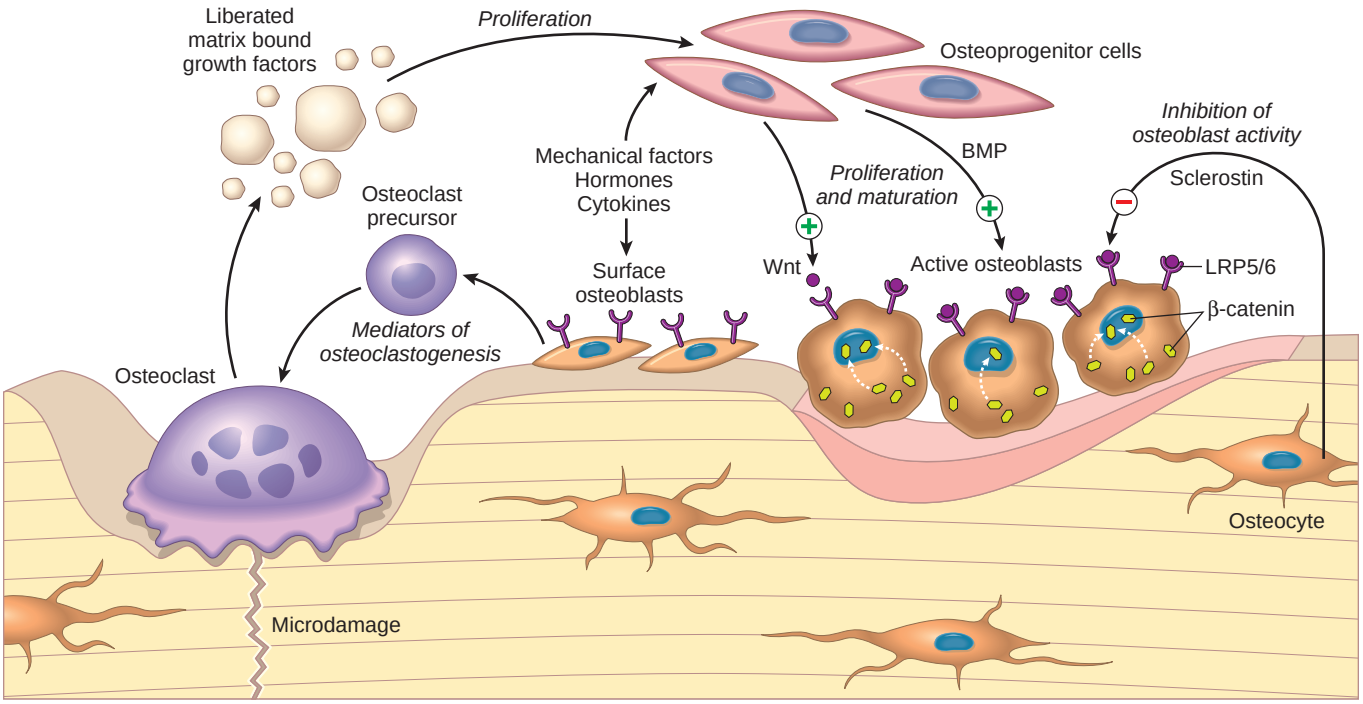

Figure 26-5 Bone cells and their interrelated activities. Hormones, cytokines, growth factors, and signal-transducing molecules are instrumental in their formation and maturation, and allow communication between osteoblasts and osteoclasts. Bone resorption and formation in remodeling are coupled processes that are controlled by systemic factors and local cytokines, some of which are deposited in the bone matrix. BMP, bone morphogenic protein; LRP5/6, LDL receptor related proteins 5 and 6.

and glucocorticoids), vitamin D, inflammatory cytokines (e.g., IL-1), and growth factors (e.g., bone morphogenetic factors). Each of the above presumably acts by altering the levels of RANK/NF-κB and WNT/β-catenin signaling in osteoblasts. The mechanisms are complex, but parathyroid hormone, IL-1 and glucocorticoids promote osteoclast differentiation and bone turnover. In contrast, bone morphogenic proteins and sex hormones generally block osteoclast differentiation or activity by favoring OPG expression.

Another level of control involves paracrine crosstalk between osteoblasts and osteoclasts. Breakdown of matrix by osteoclasts liberates and activates matrix proteins, growth factors, cytokines, and enzymes (e.g., collagenase), including some that stimulate osteoblasts. Thus, as bone is broken down to its elemental units, substances are released into the microenvironment that initiate its renewal (Fig. 26-5).

Peak bone mass is achieved in early adulthood after the cessation of skeletal growth. This set point is determined by a variety of factors, including polymorphisms in the receptors for vitamin D and LRP5/6, nutrition, physical activity, age, and hormonal status. Beginning in the fourth decade, however resorption exceeds formation, so there is a steady decline in skeletal mass.

Developmental Disorders of Bone and Cartilage

Developmental abnormalities of the skeleton are frequently the result of inherited mutations and first become manifest during the earliest stages of bone formation. In contrast, acquired diseases are usually detected in adulthood. The complexity of the skeleton's growth, development, maintenance, and relationships with other organ systems makes it unusually vulnerable to adverse influences. The spectrum of disorders of bone development is broad and the classification system is not standardized. Here we will categorize the major diseases according to their perceived pathogenesis.

Developmental anomalies can result from localized problems in the migration and condensation of mesenchyme (dysostosis) or global disorganization of bone and/or cartilage (dysplasia). Dysostoses are usually limited to defined embryologic structures and may occur in isolation or as part of more complex syndromes. They result from defects in the formation of the mesenchymal condensations and their differentiation into the cartilage anlage. The most common forms include complete absence of a bone or entire digit *(aplasia)*, extra bones or digits *(supernumerary digit)*, and abnormal fusion of bones (e.g., *syndactyly, craniosynostosis*). Genetic alterations that affect transcription factors, especially those encoded by the homeobox genes, cytokines and cytokine receptors, are especially common among the dysostoses. In contrast, dysplasias arise from mutations in genes that control development or remodeling of the entire skeleton. It is important to note that the term dysplasia in this context simply implies abnormal growth rather than a premalignant lesion as used in the context of neoplasia (Chapter 7).

More than 350 skeletal dysostoses and dysplasias, most extremely rare, have been recognized. The classification has evolved from purely clinical and radiographic