- Thyroid hormone (T3) is secreted by the thyroid gland, and acts on proliferating chondrocytes to induce hypertrophy.
- Indian hedgehog (Ihh) is a locally secreted regulator, made by prehypertrophic chondrocytes, that coordinates chondrocyte proliferation and differentiation and osteoblasts proliferation.
- Parathyroid hormone related protein (PTHrP) is a local factor, expressed by perichondrial stromal cells and early proliferating chondrocytes, that activates the PTH receptor and maintains proliferation of chondrocytes.
- Wnt is a family of secreted factors that are expressed at highest levels in the proliferating zone and bind to the receptors Frizzled and LRP5/6 to activate β-catenin signaling. They can promote both proliferation and maturation of chondrocytes.
- SOX9 is a transcription factor expressed by proliferating but not hypertrophic chondrocytes that is essential for differentiation of precursor cells into chondrocytes.
- RUNX2 is a transcription factor involved in chondrocyte and osteoblast differentiation. It is expressed in early hypertrophic chondrocytes and immature mesenchymal cells and controls terminal chondrocyte and osteoblast differentiation, respectively.
- Fibroblast growth factors (FGFs) are secreted by a variety of mesenchymal cells. FGF (most notably FGF3) acts on hypertrophic chondrocytes to inhibit proliferation and promote differentiation.
- Bone morphogenic proteins (BMPs) are members of the TGF-β family. They are expressed at various stages of chondrocyte development in the growth plate and have diverse effects on chondrocyte proliferation and hypertophy.

Homeostasis and Remodeling

The adult skeleton appears static but is actually constantly turning over in a tightly regulated process known as remodeling. Approximately 10% of the skeleton is replaced annually. This process can repair microdamage or change the shape of bones in response to structural and mechanical demands. Remodeling takes place at a microscopic locus known as the bone (or basic) multicellular unit (BMU), which consists of a unit of coupled osteoblast and osteoclast activity on the bone surface. An orderly sequence of osteoclast attachment, resorption, osteoblast attachment and proliferation and, finally, matrix synthesis proceeds at the BMU.

The events at the bone multicellular unit are regulated by cell-cell interactions and cytokines. The control mechanisms are not known completely, but several signaling pathways of particular importance have emerged (Fig. 26-4). One such pathway involves three factors: (1) the transmembrane receptor RANK (receptor activator for NF-κB), which is expressed on osteoclast precursors; (2) RANK ligand, (RANKL) which is expressed on osteoblasts and marrow stromal cells; and (3) osteoprotegerin (OPG), a secreted "decoy" receptor made by osteoblasts and several other types of cells that can bind RANKL and thus prevent its interaction with RANK. When stimulated by RANKL, RANK signaling activates the transcription factor

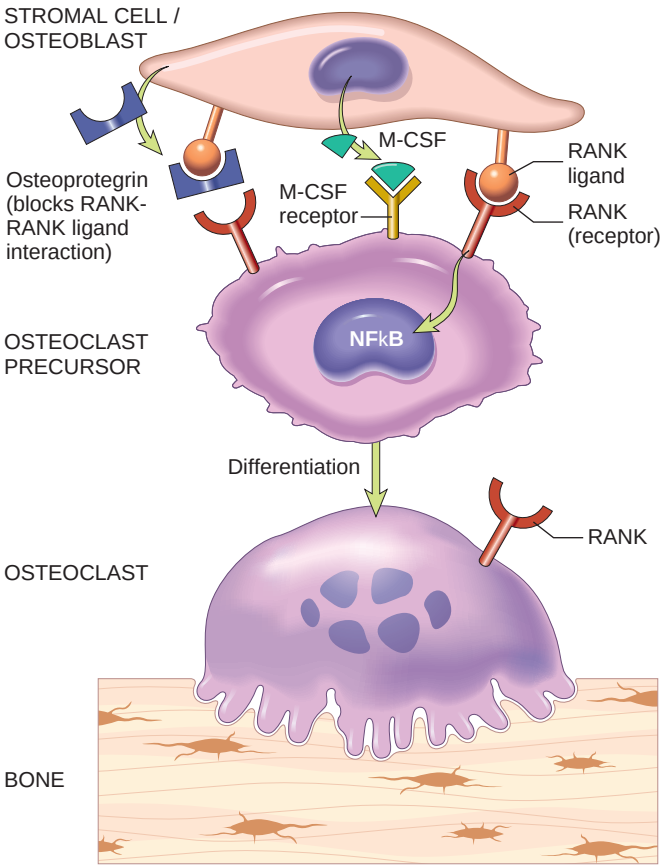

Figure 26-4 Paracrine molecular mechanisms that regulate osteoclast formation and function. Osteoclasts are derived from the same mononuclear cells that differentiate into macrophages. Osteoblast/stromal cell membrane-associated RANKL binds to its receptor RANK located on the cell surface of osteoclast precursors. This interaction in the background of macrophage colony-stimulating factor (M-CSF) causes the precursor cells to produce functional osteoclasts. Stromal cells also secrete osteoprotegerin (OPG), which acts as a "decoy" receptor for RANKL, preventing it from binding the RANK receptor on osteoclast precursors. Consequently, OPG prevents bone resorption by inhibiting osteoclast differentiation.

NF-κB, which is essential for the generation and survival of osteoclasts. A second important pathway involves monocyte colony stimulating factor (M-CSF) produced by osteoblasts. Activation of the M-CSF receptor on osteoclast precursors stimulates a tyrosine kinase cascade that is also crucial for the generation of osteoclasts. Also notable is the WNT/β-catenin pathway. WNT proteins produced by osteoprogenitor cells bind to the LRP5 and LRP6 receptors on osteoblasts and thereby trigger the activation of β-catenin and the production of OPG (Fig. 26-5). Conversely, sclerostin, which is produced by osteocytes, inhibits the WNT/β-catenin pathway. The importance of these pathways is proven by rare but informative germline mutations in the *OPG, RANK, RANKL,* and *LRP5* genes, which cause severe disturbances of bone metabolism (described later).

The balance between net bone formation and resorption is modulated by the signals that connect to the RANK and WNT signaling pathways. For example, because OPG and RANKL oppose one another, either bone resorption or bone formation can be favored by tipping the RANK-to-OPG ratio. Systemic factors that affect this balance include hormones (parathyroid hormone, estrogen, testosterone,