Control of Osteoclasts as a Therapeutic Approach to Osteoporosis and Other Bone Diseases

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Bone homeostasis is maintained by a balance in the activity of osteoblasts, bone forming cells, and that of osteoclasts, bone-resorbing cells. Osteoclasts are derived from hematopoietic stem cells whereas osteoblasts are generated from mesenchymal stem cells through a complex differentiation program. The differentiation, activation, and life span of osteoclasts have been shown to be regulated by various factors including cytokines. Recently, many studies have provided ample evidences that the tumor necrosis factor (TNF) family member RANKL (receptor activator of NF- κB ligand; also known as ODF, OPGL, and TRANCE), expressed on the surface of osteoblasts/stromal cells, plays an essential role for osteoclast differentiation by binding to its receptor RANK on the surface of osteoclast precursor cells. In addition, the RANK-RANKL interaction stimulates the activity and cell survival of differentiated osteoclasts. Osteoprotegerin (OPG) is a decoy receptor that interferes with RANKL binding to RANK. The RANK signaling mechanisms involved in osteoclast responses include the recruitment of TNF receptor-associated factor proteins, the activation of transcription factors (NF- B, AP-1, and NFAT2), the cascades of mitogen-activated protein kinases (ERK, JNK, and p38), and the induction of Src- and phosphatidylinositol 3-kinase-dependent Akt activation. Proinflammatory cytokines such as TNF and IL-1 also have potent effects on differentiation, activation, and survival of osteoclasts. Several molecules playing a key role in osteoclast differentiation and activation have been a target of drug development for osteoporosis and other bone loss-associated diseases. For example, bisphophonates block prenylation of small G proteins in and induce apoptosis of osteoclasts. Calcitonin suppresses osteoclast activation without affecting its differentiation. Recent advance in the development of protein drugs targeting the RANK-RANKL-OPG system has drawn a great attention. Discovery of new molecules crucially and specifically involved in osteoclast differentiation and activation will provide new targets for development of bone disease therapeutics. Systemic and global approaches employing genomics and proteomics tools may be an effective means for identification of diverse target molecules.