Osteoprotegerin: a novel local player in bone metabolism

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The clinical consequences of impaired bone remodeling and the concept of orchestrated bone formation and resorption are now well appreciated. However, the factors responsible for increased (osteopetrosis) or decreased (osteoporosis) bone mass are still poorly identified, and knowledge about local mediators of cross-talk between osteoblasts and osteoclasts has remained scarce. Theoretically, an imbalance between bone formation and resorption may result from a variety of defects such as altered proliferation of uncommitted precursor cells, impaired recruitment of progenitor cells, and poor differentiation towards the mature phenotype in both the osteoblast and osteoclast lineages (1–3). Potential candidates mediating bone remodeling include cytokines such as monocytetumor necrosis factor-α (TNF-α) and interleukins (IL)-1, -6, and -11, all of which, following activation of their respective receptors, are known to promote osteoclastogenesis (1, 3, 4). Expression of these cytokines is regulated by a variety of calcitropic and sex steroid hormones as well as by a complex network of other cytokines and growth factors (1, 5, 6). In addition, various endogenous cytokine antagonists (e.g. IL-1 receptor antagonist) and soluble receptor forms (e.g. sIL-1 receptor) may act to modulate the actions of these cytokines within the bone microenvironment. However, a direct role for any one of these cytokines as a regulator of remodeling has been questioned, in part because some of the observed effects have not been consistent among different species, and the methods used (overexpression resulting from transgenic animals or stable transfection of cell lines; generation of knock-out animals) have failed to establish unambiguously a cause–effect relationship.

In a large interdisciplinary group effort published in Cell (7), Simonet and co-workers have recently identified a novel secreted glycoprotein named osteoprotegerin (OPG) which appears to be a crucial factor capable of regulating bone remodeling. Based on sequence comparison following screening of a fetal rat intestine cDNA library, OPG was initially discovered as a member of the TNF receptor (TNFR) superfamily. However, in contrast to other members of this family, OPG is unlikely to be a membrane-anchored receptor since it lacks transmembrane domain structures. This suggests that, following its secretion, OPG may act within the extracellular space. Thus, while OPG, a disulfide-linked dimer of 110 kDa, has four tandem cysteine-rich TNFR motifs at the N-terminus, its C-terminus is unrelated to any known protein. Intriguingly, transgenic mice overexpressing OPG display a form of non-lethal osteopetrosis that is characterized by both increased bone density and decreased osteoclast differentiation (7). Moreover, exogenous administration of OPG has been shown to inhibit osteoclast differentiation in an in vitro assay. In addition, administration of recombinant OPG increased bone density in normal mice, and protected rats against ovariectomy-induced bone loss to an extent similar to the administration of the bisphosphonate pamidronate. Although the primary source of OPG production remains to be determined, in situ hybridization in a mouse embryo revealed OPG mRNA expression in, among others, the cartilagenous aspects of bone (7), suggesting that OPG is, in fact, a local osteoclast inhibitor of as yet unknown origin.

While these data strongly and convincingly establish a pivotal role for OPG in bone remodeling, the mechanisms by which OPG acts are unknown. Conceptually, the TNFR portion of OPG may represent an endogenous, soluble form of TNFR that is secreted into the extracellular bone matrix where it acts in an autocrine and paracrine fashion. This soluble receptor may then compete with membrane-bound TNFR for its ligand, thus neutralizing the biological effects of TNF-α or TNF-related proteins which are involved in cell cytotoxicity, apoptosis, and cell survival (8, 9). OPG may thus represent a naturally occurring cytokine antagonist similar to the IL-1 receptor antagonist. Two recent studies employing a similar approach support this ‘TNF-α agonist/antagonist’ theory of maintenance of bone mass. In the first study, transgenic mice overexpressing soluble TNFR, which neutralizes TNF-α, were protected against bone loss caused by estrogen deficiency (10). In the second study, ovariectomy-induced bone loss in normal mice could be prevented by treatment with TNF-binding protein which inhibits TNF-α action by competing with TNFFR for its ligand (11). By contrast, no such effect was observed after a functional block of IL-6 had been exerted (11). Taken together, these studies, along with the discovery of OPG, support the hypothesis that OPG may act to prevent bone loss by counterbalancing the bone-resorptive actions of TNF-α. Intriguingly, the human gene for OPG is located on chromosome 8q23–24, a locus close to a candidate gene for hereditary multiple exostosis
and certain forms of chondrosarcoma, as well as the gene encoding bone morphogenetic protein-1 (7, 12). To corroborate a physiological and pathophysiological role for OPG, future studies will have to address its production site, its regulation by calcitropic and other hormones (e.g. estrogens, androgens), and its molecular mechanism of action, all of which could lead to a better understanding of the pathogenesis of metabolic bone diseases.

References
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