EDITORIAL COMMENT

Skeleton Key to Vascular Disease*

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Bone biology has developed increasing importance in vascular biology, and vice versa. The link begins in the embryo, when bone develops on a vascular reticulum produced by angiogenic ingrowth into calcified cartilage. The connection remains in late adulthood, when bone tissue forms within atherosclerotic arteries. Epidemiologically, atherosclerosis and osteoporosis are closely correlated, even when adjusted for age and gender (1). Loss of bone in the skeleton occurs simultaneously with formation of bone in the arterial wall, raising important questions about mechanisms and current treatments. For example, do calcium supplements promote vascular mineralization as much or even more than bone mineralization? One possible explanation for these concomitant but opposite processes is that bone and vascular tissues have opposite responses to the same stimulus. In fact, there is evidence that both disorders are associated with hyperlipidemia (2), hypovitaminosis K, and hypervitaminosis D (3–5). More recent investigation of the relationship between osteoporosis and vascular calcification has focused on the role of bone proteins in vascular calcification and osteoporosis. Proteins initially characterized in bone, including osteopontin (6,7), osteocalcin, bone morphogenetic protein-2 (8), matrix gamma-carboxyglutamic acid protein (9), receptor activator of nuclear factor kappa B (RANK-L) (10), and osteoprotegerin (10,11), are also present in atherosclerotic plaques, and they are expressed by vascular cells in situ and in vitro. Much has been learned about the function of some, but the roles of others remain enigmatic. The overall picture remains incomplete.

In this issue of the Journal, Ueland et al. (12) present data correlating the baseline plasma level of the bone protein osteoprotegerin (OPG) with survival and cardiovascular events in 234 patients surviving an acute myocardial infarction (MI). The patients were selected for this substudy from a trial comparing losartan versus captopril after MI. The OPG levels in these patients were significantly higher than those in a cohort of healthy, age-matched control subjects. After a mean follow-up of about three years, 32 of the patients died. These patients had a significantly higher baseline OPG level than survivors. After adjustment for confounding variables, patients in the highest quartile of OPG levels had an increased risk for mortality, as well as for a composite end point of mortality, nonfatal MI, and stroke. These results suggest that elevated OPG may be a useful marker for a poor prognosis in patients with acute coronary syndromes complicated by heart failure.

By what mechanism could this bone-regulatory factor influence cardiovascular disease? Bone protein OPG is one of a trio of powerful interacting molecules now known to regulate bone turnover. For decades, bone biologists knew that differentiation of bone-resorbing osteoclasts from monocytes required the presence of bone-forming osteoblasts, and that osteoclastic activity was carefully balanced and coupled with osteoblastic activity. The essential factor provided by the osteoblasts was ultimately identified as RANK-L (Table 1). RANK-L on osteoblasts binds its receptor (RANK), (13) a member of the tumor necrosis factor (TNF) receptor superfamily, on the surface of osteoclast precursors, including monocytes and macrophages. The RANK-L binding to RANK activates nuclear factor-kappa B, which, in turn, translocates to the nucleus and activates the Akt/protein kinase B cell survival pathway. Bone protein OPG is the third member of this trio, a secreted glycoprotein, which was found to act as a soluble decoy receptor for the RANK ligand, competing and preventing activation of RANK on osteoclasts (Fig. 1). Thus, OPG inhibits osteoclast differentiation, and, as expected, can inhibit forms of osteoporosis.

Also as expected, elimination of OPG gene expression, as in OPG-deficient mice, results in osteoporosis with increased osteoclast activity. However, these mice also have the unexpected phenotype of vascular calcification (14). The coexistence of osteoporosis and vascular calcification in OPG knockout mice has raised interest in the possibility that OPG underlies the clinical link between these two entities. Based on the vascular phenotype, it is natural to expect that OPG should protect the vasculature.

The situation is not simple, however, as indicated by the data from Ueland et al. (12), showing a positive association between elevated OPG levels and poor cardiovascular prognosis. In addition, others have shown that OPG levels are elevated in patients with angiographic coronary artery disease (15,16), and they correspond to progression of carotid atherosclerosis and development of clinically significant coronary artery disease (17).

One possible explanation for this apparent paradox lies in the effects of OPG on inflammation. First, by interfering with RANK-L and possibly other members of the TNF family signaling pathway, it blocks some aspects of inflammation. In addition, OPG may block another role of RANK-L—activation of lymphocyte differentiation and function. Under normal conditions, RANK-L is most highly expressed in lymph node tissue (18), and it enhances activated T-cell survival (19). Mice deficient in RANK-L
have no lymph nodes and abnormal B- and T-cell differentiation (20). In peripheral blood monocytes, RANK-L induces expression of a myriad of inflammatory cytokines, including TNF-alpha, interleukin (IL)-6, IL-12, IL-1-beta, and macrophage inflammatory protein-1-alpha (21). T-cell expression of RANK-L is believed to result in the clinically significant bone loss seen in association with rheumatoid arthritis.

Several lines of evidence suggest a function of OPG in vascular disease (22). Osteoprotegerin is produced in the normal artery wall (23) and in cultured arterial cells such as coronary smooth muscle cells (24) and endothelial cells (25). RANK-L and RANK are not expressed in the normal artery wall (23), but they are expressed in calcified arteries of OPG deficient mice, and they co-localize with osteoclast-like cells (23).

Interestingly, elevated serum OPG may be due to high RANK-L levels. Mice treated with RANK-L have elevated serum OPG levels, suggesting a compensatory response to the effect of RANK-L as part of a negative feedback loop. For example, IL-2–deficient mice develop profound osteopenia and inflammatory colitis associated with hyperactivated T lymphocytes. At four weeks, serum RANK-L levels are elevated but fall to normal by nine weeks, whereas serum OPG is normal at four weeks but rises precipitously by nine weeks. These effects are eliminated by administration of recombinant OPG at four weeks (26). This example illustrates the concept that the OPG level alone is not sufficient to understand its role in pathophysiology; the relative amount of RANK-L is just as or possibly more important.

Osteoprotegerin may produce even more complex phenomena through its effects on other members of the TNF family. Soluble CD40 ligand, which is closely related to the RANK-L (18), is also an independent marker for adverse outcomes in patients with acute coronary syndromes (27). Activation of CD40 increases expression of OPG (28). In addition, OPG confers protection from endothelial apoptosis (6). These multiple effects support the concept advanced by Ueland et al. (12) that OPG is not merely a biomarker of inflammation.

Finally, it would not be surprising to find a marker of heart failure that is also an effective therapy. An example of this is brain natriuretic peptide. It is difficult to assign a “white hat” or “black hat” categorization to OPG. A more complete picture is needed, and rational therapy will need to take into consideration, at the least, both vascular and skeletal pathophysiology.

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REFERENCES

Table 1. Nomenclature for the OPG/RANK/RANKL System

<table>
<thead>
<tr>
<th>Factor</th>
<th>Alternate Names</th>
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<tbody>
<tr>
<td>Osteoprotegerin (OPG)</td>
<td>Osteoclast inhibitory factor (OCIF)</td>
</tr>
<tr>
<td>Receptor activator of nuclear factor-kappa B ligand (RANK-L)</td>
<td>Osteoprotegerin ligand (OPGL)</td>
</tr>
<tr>
<td>RANK</td>
<td>Tumor necrosis factor–related activation-induced cytokine (TRANCE)</td>
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<tr>
<td></td>
<td>Osteoclast differentiation factor (ODF)</td>
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<td>Osteoclast differentiation factor receptor (ODFR)</td>
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Figure 1. Schematic illustrating the interaction of osteoprotegerin (OPG) with RANK and the receptor activator of nuclear factor-kappa B ligand (RANK-L). Osteoprotegerin acts as a soluble decoy receptor, blocking interaction of RANK-L with its receptor, RANK.


