PERSPECTIVE

A New Insight into the Formation of Osteolytic Lesions in Multiple Myeloma

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Multiple myeloma is a cancer in which immunoglobulin-producing plasma cells undergo clonal expansion. Its characteristic feature is the monoclonal, or M, spike, usually detectable in serum or urine by protein electrophoresis. Malignant plasma cells have complex chromosomal rearrangements, leading in many cases to the aberrant activation of gene expression. Some of these activated genes encode secreted factors that can modify the microenvironment of the tumor in a manner that favors its growth or promotes its ability to cause lesions in surrounding tissues. The mechanism of bone destruction, a feature of multiple myeloma, is the focus of the article by Tian et al. in this issue of the *Journal* (pages 2483–2494).

A major determinant of morbidity in multiple myeloma stems from its residence in bone. Within the microenvironment of bone, the malignant cells instigate focal areas of severe bone loss; patients typically present with numerous "punched-out" osteolytic lesions, which cause bone pain, pathologic fractures, and hypercalcemia. The pathogenesis of these focal lesions is thought to be due to the dysregulation of bone remodeling, a process that is the basis of the important findings of Tian et al.

The skeleton constantly undergoes remodeling, in which bone resorption is followed by bone formation. During bone resorption, osteoclasts attach to the bone surface and secrete proteases and collagenases that degrade the bone matrix. After resorption, osteoblasts migrate to the recently resorbed area and lay down new bone matrix. A functional balance must be maintained between resorption and formation to keep bone mass constant.

An imbalance in favor of net bone resorption (through increased osteoclast activity, decreased osteoblast activity, or both) leads to osteopenia, or low bone mass. The focal osteolytic lesions in multiple myeloma are due to aberrant osteoclast activity, as illustrated by the efficacy of bisphosphonates, a group of compounds that inhibit osteoclast function, in blocking the formation of focal lesions. Despite bisphosphonate treatment, however, there is no increase in bone deposition by osteoblasts within the lytic lesions, suggesting that the functions of both osteoblasts and osteoclasts are perturbed in multiple myeloma.

Bone resorption is regulated by hormones and local cytokines. A particularly important mode of regulation entails two secreted factors, the receptor activator of nuclear factor-κB ligand (RANKL) and its soluble antagonist, osteoprotegerin, which are secreted by a variety of cells, including osteoblasts. When RANKL binds to receptors on osteoclast precursors, it stimulates the differentiation, activation, and function of osteoclasts. Recent work has demonstrated that serum levels of RANKL are increased in multiple myeloma, as are the expression of the *RANKL* gene and the degradation of osteoprotegerin by myeloma cells. These findings suggest that direct stimulation of osteoclast activity causes the lytic lesions of multiple myeloma (see Figure).

Unlike bone resorption, cytokine-mediated regulation of bone formation is not well understood. Mutations in the gene for low-density lipoprotein receptor–related protein 5 (LRP5), which encodes a coreceptor for signaling by the Wnt family of growth factors, lead to either a high bone mass or a low bone mass, depending on the mutation. Secreted Wnt glycoproteins constitute a major cell-to-cell signaling family that can control nearly all aspects of cellular biology during development and beyond. In the classic, or canonical, Wnt-signaling pathway, a Wnt growth factor must bind to both its receptor and either an LRP5 or an LRP6 coreceptor to initiate signaling. This step initiates a series of biochemical events within the cell that result in the stabilization of cytoplasmic β-catenin, which is now free to trans-

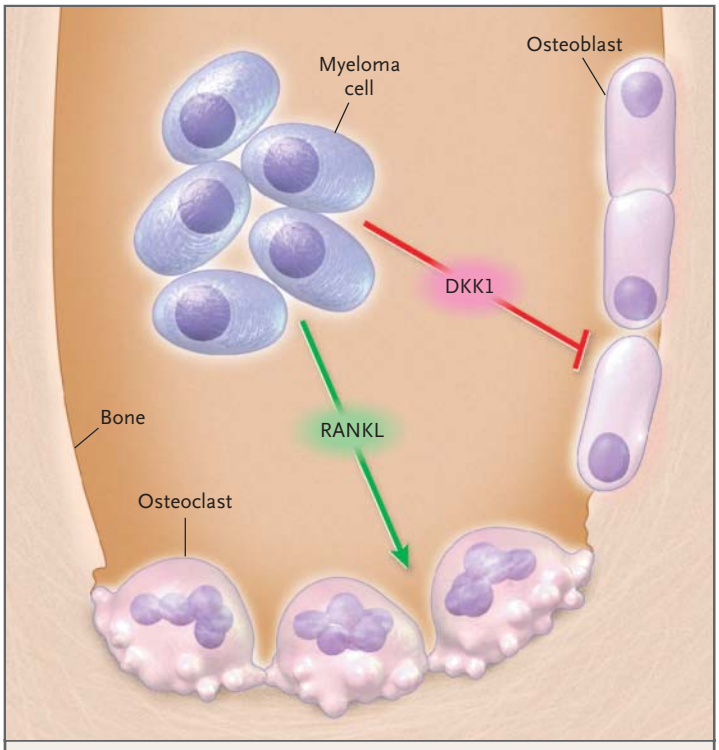

Figure. Pathogenesis of Lytic Lesions in Multiple Myeloma.

Myeloma cells secrete at least two molecules that modulate the bone microenvironment in a manner favorable to tumor growth. Receptor activator of nuclear factor-κB ligand (RANKL) acts to stimulate osteoclast formation and activity leading to bone erosion, whereas dickkopf1 (DKK1) appears to inhibit osteoblasts, thus preventing repair of the lesions.

locate into the nucleus and turn on Wnt-responsive genes. This process can be hampered by Wnt inhibitors that bind extracellular Wnt ligands. Other soluble molecules such as dickkopf1 (DKK1), the focus of the article by Tian et al., bind to the Wnt coreceptor LRP5 and thereby prevent Wnt signaling.

In comparing the gene-expression profiles of myeloma cells from patients who had focal osteolytic lesions with the profiles of myeloma cells from patients who did not have detectable bone lesions, Tian et al. found that the *DKK1* gene was overexpressed in patients with focal lesions. In bone marrow–biopsy specimens from the two groups of patients and control subjects, they found that only myeloma cells contained detectable DKK1. In addition, elevated levels of DKK1 in peripheral blood and plasma from bone marrow aspirates were associated with the presence of focal osteolytic lesions. These data suggest that the overexpression of *DKK1* by myeloma cells is involved in the generation and maintenance of the focal osteolytic lesions of multiple myeloma (see Figure). Though these lesions are due to aberrant osteoclast activity, Tian et al. provide preliminary evidence that DKK1 acts to inhibit the activity of osteoblasts.

Using an in vitro system based on an immortalized mesenchymal cell line that can differentiate into osteoblasts, Tian et al. show that the presence in the culture of recombinant DKK1 or of bone marrow plasma containing elevated DKK1 levels inhibits osteoblast differentiation. Therefore, it appears that myeloma cells secrete not only RANKL, which enhances osteoclast activity, but also DKK1, which hinders osteoblasts, thus selectively biasing the remodeling process by inhibiting bone formation. Knowledge of this mechanism helps us to understand how lytic lesions are maintained in patients with myeloma and why osteoblasts do not replace lost bone during bisphosphonate treatment in such patients, despite the inhibition of osteoclasts.

The elevated serum levels of DKK1 and RANKL in patients with myeloma may act systemically and thus contribute to the diffuse osteopenia and hypercalcemia that frequently accompany this condition. Ameliorating the bone-specific morbidity of multiple myeloma by the administration of an antibody against DKK1 is one potential therapeutic approach. The next few years may provide us with additional discoveries that implicate Wnt signaling in the pathogenesis of other bone diseases.

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