

## MEETING REPORTS

### Cancer and Bone: Meeting Report from the 33<sup>rd</sup> Annual Meeting of the American Society for Bone and Mineral Research

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Presentations concerning cancer and the skeleton were distributed throughout the oral and poster program of the 2011 Annual Meeting of the American Society for Bone and Mineral Research, reflecting the importance of research on the bone microenvironment in supporting the establishment and growth of solid and hematological malignancies. It was also encouraging to see a revival of interest in studies of osteosarcoma, the primary malignancy of bone and a devastating childhood disorder.

In the case of metastatic bone disease, many papers addressed the ways in which increased bone resorption favors bone metastatic growth; a few of these studies that introduced promising new ideas are summarized here. Hurchla *et al.* identified Hedgehog (Hh) inhibitors as anti-metastatic agents (1). Genetic and drug inhibition of the receptor Smoothened (SMO) inhibited bone resorption and bone metastasis of a mouse cancer. There was also evidence of an anti-tumor effect of inhibiting Hh signaling, but some human cancers, including those of the breast, are SMO-negative. Nevertheless, the Hh pathway is worthwhile pursuing in preclinical studies, while keeping in mind the importance of knowing how frequently the Hh signaling pathway is operative in human cancers.

MDA-MB-231 human breast cancer cells have been used extensively for years, particularly because of their ability to grow as lytic deposits in bone after intracardiac injection in nude mice. That approach contributed much to the development of the concept of the "vicious cycle." The latter has been focused on tumor production of parathyroid hormone-related protein

(PTHrP), augmented by TGF- $\beta$  derived from bone matrix during resorption, and enhancing PTHrP production and perhaps also osteoclast production. There are many other tumor-derived contributors, though, including interleukin (IL)-11, IL-8, macrophage colony-stimulating factor (M-CSF), and monocyte chemoattractant protein-1 (MCP-1). Zheng *et al.* treated MDA-MB-231 cells *in vitro* with RANKL, resulting in increased IL-6 production, which in turn enhanced production of the receptor, RANK, by the cancer cells (2). When IL-6 expression was silenced with short hairpin RNA (shRNA) or when treatment with anti-IL-6 antibody was provided, tumor cell invasion was reduced *in vitro*, and bone deposit growth *in vivo* was reduced after intratibial implantation of MDA-MB-231 cells, while no effect was found on tumor growth after mammary fat pad implantation. This assigns to the cancer cell itself another way of influencing tumor-host interaction, responding to bone-derived RANKL by initiating a cycle of cooperation between tumor-derived IL-6 and RANK to enhance tumor growth in bone. This is particularly interesting because it suggests a specific role for RANK signaling in the cancer cell in bone—something that has been elusive thus far, but which might not be surprising in view of recent discoveries of a central role for RANKL/RANK signaling in mammary stem cell development (3-5).

Another new approach with this model came from Eleftheriou *et al.* (6). Based on clinical evidence that psychosocial stress enhances breast cancer morbidity and mortality, these investigators tested the effect of sympathetic nervous system (SNS) activation on bone colonization and growth of MDA-MB-231 cells after intracardiac injection.  $\beta$ -

adrenergic stimulation enhanced tumor cell migration *in vitro* by a RANK-dependent mechanism, and then in a model of chronic stress induction in mice, colonization and growth of tumors in bone were enhanced after intracardiac injection, with these effects prevented by pharmacological  $\beta$ -adrenergic blockade. Since SNS stimulation enhances resorption and as expected, increases tumor growth in bone because of that, the focus in this work is on whether SNS activation enhances the very earliest stages of bone colonization by tumors. This brings us toward a new aspect of bone metastasis pathogenesis, and progress in this area will rely heavily on improved methods for detecting early events, which this group is developing.

One of the most exciting new findings—prevention of tumor growth and bone destruction in myeloma by Pim kinase inhibition—was reported by Hiasa *et al.* (7), based on their evidence that the threonine-serine kinase, Pim-2, is a critical survival factor in leukemia (8). Inhibition of Pim kinase either by small interfering RNA (siRNA) or by a drug inhibitor, SMI-16a, enhanced osteoblast differentiation and increased calvarial bone formation *in vitro*, with a mechanism indicating potentiation of bone morphogenetic protein (BMP)-2 signaling. Using a novel model in which myeloma cells were grown in the marrow cavities of rabbit bones explanted in SCID-rab mice, the drug inhibitor treatment resulted in dramatic reduction of the extensive bone destruction seen in control animals. This is an attractive combination of a new critical kinase regulatory pathway and a novel experimental method, with new ideas to test in myeloma research.

Myeloid-derived suppressor cells (MDSCs) received attention as contributors to the bone growth of malignancy. Capietto *et al.* showed that MDSCs inhibited CD8<sup>+</sup> T cells, thus promoting the growth of tumors in the bones of mice, and were effective in doing so even when they were grown in mice with some degree of genetically-induced osteopetrosis (9). Park *et al.* used PC-3 prostate cancer lines low and high in PTHrP production to show that tumor-derived PTHrP expands the marrow MDSC

population, and that these cells return to the tumors to enhance tumor angiogenesis and growth (10). Clearly there is value in exploring further how the MDSC population might facilitate tumor growth, primary or metastatic, through effects on angiogenesis and immune suppression.

Experimental osteosarcoma (OS) is at last receiving increased attention. A new experimental model came from Tao *et al.* (11), who made use of the observation that *p53(-/-)* OS samples have enhanced Notch signaling (12). Mice in which they transgenically overexpressed Notch developed osteosclerosis at about 2 months, reflecting enhanced osteoblast proliferation but reduced differentiation. When the transgene was bred into a *p53*-null background, mice developed OS with a mean latency of 5 months. This new model focuses upon a *p53*-Notch interaction in OS pathogenesis, and is a valuable addition to other recently developed models (5;13) that will allow testing of drug treatments and progress towards identification of new drug targets.

Although there were a number of items of interest throughout the 2011 Annual Meeting of the ASBMR, the opinion of this commentator is that cancer and the skeleton does not get the attention it deserves in this forum. Of course this largely depends on the abstracts that are submitted, so we need to encourage investigators in this area, given the extraordinarily interesting biology that operates in the course of solid and blood malignancies interacting with the microenvironment of bone.

**Conflict of Interest:** None reported.

**Peer review:** This article has been peer-reviewed.

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