THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

CMBD

CENTER FOR METABOLIC BONE DISEASE

DIRECTOR'S NOTES

I officially stepped down as Chair of Pathology at UAB on September 1, 2008. Kevin A. Roth, MD, PhD, a long-term associate of mine, replaced me and will be an excellent Chair. I will continue as the CMBD Director, PI of both the NIH P30 Research Core Center Grant and T32 Institutional Training Grant, Associate Director of the UAB Center for Clinical and Translational Science, director of my own research program, provide pathology services at the VA and assist the UAB Research Foundation by working at the interface between it and the UAB faculty. I look forward to continuing my existing research and service responsibilities and to beginning my new responsibilities with the UAB Research Foundation.

The annual American Society for Bone and Mineral Research meeting was held September 12-16, 2008, in Montréal, Québec, Canada. Once again UAB was well represented, including 9 oral presentations and 32 poster presentations by CMBD members. This was an increase of 8 over last year and represented 2.2% of all official presentations at the meting.

Below is an overview of bone disease in multiple myeloma written by Ralph D. Sanderson, PhD, Professor, Department of Pathology.

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Bone Disease in Multiple Myeloma

Multiple myeloma is a fatal malignancy comprised of clonal plasma cells. In many cases the disease is marked by extensive osteolytic bone disease that can result in bone fracture, hypercalcemia, compression of the spinal cord, osteoporosis and persistent, debilitating bone pain. Although the causes of bone destruction in myeloma are still being unraveled, there is an apparent uncoupling between bone resorption and bone formation resulting in a net loss of bone. This dysregulation occurs due to cross-talk between tumor and host cells that causes upregulation of osteoclast numbers and activity and downregulation in osteoblast numbers and activity. Additionally, factors released during the osteolytic process stimulate further growth and metastasis of the tumor cells.

A number of soluble factors have been implicated in regulating myeloma bone disease. RANKL, TNF, lymphotoxin, MIP-1α and SDF-1 all have a role in stimulating osteoclasts thereby driving osteolysis. For example, RANKL levels are elevated in myeloma patients due to increased expression by marrow cells and osteoblasts as well as by myeloma tumor cells themselves. Additionally, OPG, the decoy receptor for RANKL, is downregulated in the myeloma microenvironment thereby effectively enhancing RANKL-stimulated osteoclast formation and activity. Additional factors elaborated as a consequence of myeloma tumor growth include DKK1, IL-3, HGF and TGF-β, all of which are thought to inhibit osteoblastogenesis thus diminishing new bone formation. DKK1 has recently received a lot of attention in the myeloma field because it is present in high levels in many myeloma patients and is associated with bone disease. DKK1 acts as a powerful antagonist of Wnt signaling, a pathway known to be critical in regulating bone mass. Initial studies designed to block DKK1 activity in animals of myeloma have shown efficacy in reducing both the number of osteolytic lesions and overall tumor burden. A detailed discussion of the soluble factors involved in regulation of myeloma bone disease can be found in this recent review (*Bone* 2008;42:1007-1013).

Our laboratory has for a number of years studied the role of heparan sulfate proteoglycans and heparanase in regulating myeloma growth and metastasis. Heparanase, an enzyme that degrades heparan sulfate chains, is upregulated in many myeloma patients and correlates with poor patient prognosis. Using an animal model of myeloma, we recently discovered that upregulation of heparanase expression by tumor cells leads to enhanced osteoclastogenesis and a dramatic increase in osteolysis. Moreover, we found that addition of purified recombinant heparanase to peripheral blood mononuclear can stimulate their differentiation into osteoclasts suggesting that heparanase has a direct effect on osteoclastogenesis. Our overall goal now is to determine the mechanism behind heparanase induced osteoclastogenesis and to develop and test heparanase inhibitors as anti-myeloma therapeutics.

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