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MEETING REPORTS

Mechanisms of Bone Metastasis, Pathophysiology of Osteonecrosis of the Jaw, and Integrins, Platelets and Bone Metastasis: Meeting Report from Skeletal Complications of Malignancy V

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Mechanisms of Bone Metastasis (Session 8)

TGF-β is a potent multifunctional cytokine, which inhibits the growth of normal epithelial cells and low grade tumors but promotes the growth of more advanced malignancies. TGF-β can promote breast cancer, bone metastases and may be involved in the bone metastatic process of other solid tumors (1). Recent studies have focused on the role of TGF-β in promoting renal cell bone cancer metastasis (2). Renal cell carcinoma accounts for about 30,000 cases per year and is increasing in incidence. Only 10% of the patients survive five years. Bone metastases in renal cancer are lytic with a decrease or absent osteoblastic response, analogous to the bone lesions in myeloma. Therefore, bone scans severely underestimate the extent of the disease. Renal cell carcinoma cell lines express TGF-β as well as TGF-βR1 and TGF-βRII. These results suggest that TGF-β may have autocrine effects on the growth of renal cell carcinoma cells. In support of this notion, TGF-β increases PTHrP, PDGF-AA, IL-6 and VEGF expression in renal cell carcinoma cell lines, and blocking TGF-β signaling decreases both the growth of renal cell carcinoma cells in bone as well as bone metastasis.

TGF-β may also be involved in the suppression of osteoblast activity in bone metastasis. TGF-β is an inhibitor of osteoblast differentiation but stimulates osteoblast proliferation (3). When it is overexpressed *in vivo*, TGF-β decreases bone mass by increasing osteoclast activity, and inhibiting Runx2 transcription. Smad3, which is involved in the TGF-β signaling pathway, recruits HDAC4/5 to Runx2 to block transcription. Since the amount of TGF-β signaling in osteoblasts defines the intrinsic mechanical properties of bone, partial reduction in TGF-β/Smad3 signaling should improve overall quality of bone, while local increases in TGF-β, as occur in bone metastasis, should decrease bone quality.

Further support for the important role of TGF-β in promoting bone metastasis in prostate cancer comes from studies using PC3 cells treated with a TGF-β type I receptor kinase inhibitor (4). These studies show that blocking TGF-β signaling results in decreased tumor growth, decreased bone metastasis and increased survival of animals transplanted with human prostate cancer cells. The mechanisms responsible for TGF-β's stimulating effects on prostate cancer cell growth are still unclear. One possibility is that PMEPA1 may be involved. TGF-β increases PMEPA1 expression 23-fold in prostate cancer cells, and knockdown of PMEPA1 results in decreased TGF-β signaling and inhibition of prostate cancer cell growth. However, the function of PMEPA1 is still unknown.

Pathophysiology of Osteonecrosis of the Jaw (Session 9)

Osteonecrosis of the jaw (ONJ) is an emerging complication associated with bisphosphonate therapy (5). The incidence of ONJ in patients with osteoporosis treated

with oral bisphosphonates is approximately 1:100,000/patient years in a study from Merck and 1:250,000/patient years in a study from Germany (6). The mechanisms underlying ONJ are unclear. One hypothesis for why ONJ occurs in the jaw is that bone remodeling is increased in the oral cavity, although there are no data to support this, nor do bone formation rates differ between the mandible and the humerus. Subclinical infections have been associated with ONJ and periodontal disease is a risk factor for developing bisphosphonate-associated ONJ. Histopathologic studies of ONJ have shown that in 8/8 patients studied, actinomycetes was cultured from their lesions, and 5/8 had inflammatory infiltrates. Only 1/8 patients had vessel obstruction, suggesting that ONJ is not associated with a vascular problem. Consistent with these findings that differences in the blood flow to the jaw cannot explain the occurrence of ONJ associated with bisphosphonates is that the mandible, pelvis and clavicle all have similar blood flow. Thus, currently, there are many questions, but little data or animal models available to dissect the pathophysiology of bisphosphonate-associated ONJ.

Integrins, Platelets and Bone Metastasis (Session 10)

β_3 integrins ($\alpha_v\beta_3$ and aIIbb3) play critical roles in tumor invasion and skeletal metastasis in part by mediating osteoclastic bone resorption, platelet aggregation and neo-angiogenesis (7). Bone metastases are decreased in β_3(-/-) mice. Platelets appear to play an important role in bone metastasis because platelets can surround tumor cells and allow the tumor cells to travel as micro-emboli. Anti-platelet therapy can block bone metastasis in models of metastastic melanoma. A possible mechanism for the stimulating effects of platelets on bone metastasis is that they secrete lysophosphatidic acid (LPA), which is highly mitogenic for many cancer cell types, including prostate cancer and breast cancer cells (8). LPA also enhances cancer cell survival, migration and tumor cell invasion (9). Autotaxin (ATX) is the main source of LPA in the plasma due to its lysophospholipase D (lysoPLD) activity on platelets. Expression of ATX in the MDA-BO2 breast cancer cell line increases the growth of the tumors and expression of a dominant negative ATX mutant in MDA-BO2 cells inhibited bone metastasis as well as the upregulation of IL-6, MCP-1 and IL-8 production by the breast cancer cells. These results suggest that factors in the circulation as well as changes in the bone microenvironment both contribute to the development of bone metastasis.

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