The Role of Myeloid-Derived Suppressor Cells and T-Lymphocytes in Human Vertebral Metastasis: A Prospective Pilot Study
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Tumor metastasis to bone occurs in 70% of breast cancer patients, affecting more than 70,000 patients annually. The spine is the most common location for skeletal metastasis, causing significant back pain and often spinal cord compression and paralysis. The incidence of skeletal metastasis is increasing as cancer patients have longer life expectancies – care of these skeletal metastases costs an estimated $13 billion annually in the United States. Current understanding of skeletal metastasis is incomplete, with the majority of research investigating the role of the osteoclast. However, osteoclast-focused treatments have not been highly successful in preventing or controlling bone metastasis, and thus other potential treatments must be investigated. There is growing evidence that myeloid-derived suppressor cells (MDSCs), leukocytes that mediate immunosuppression, play a key role in tumor progression and metastasis. Several studies have found that MDSCs are associated with increased metastatic tumor burden to bone in animal models, but no studies have investigated the presence and action of MDSCs in human metastatic tumors.

Our proposed research seeks to identify MDSCs in metastatic human breast adenocarcinoma in vertebral metastasis. Furthermore, we propose a novel mechanism for upregulation of MDSCs by breast cancers, via a Dickkopf-1 (DKK1) and Wnt/β-catenin pathway. We believe this work is highly clinically significant, as targeting MDSCs may prove to be an effective treatment for slowing or preventing skeletal metastases. Demonstrating that MDSCs have a role in promoting metastasis to bone will both expand the model for understanding this disease process and provide new therapeutic options for preventing and treating bone metastases.

Hypothesis:

We hypothesize that in human patients, malignant breast tumors stimulate proliferation of MDSCs in bone and peripheral blood, thereby inhibiting T-lymphocyte tumor surveillance in the bone microenvironment and facilitating skeletal metastasis. These effects are mediated by an increase in DKK1 and a decrease in β-catenin in MDSCs.

Method of Research:

Three patient groups will be enrolled: cancer-free patients, patients with non-metastatic breast cancer, and patients with known breast cancer metastases to the spine requiring surgical debulking or stabilization. Recent chemotherapy, history of bisphosphonate use, or chronic immunosuppression will exclude participation. Fifteen patients will be enrolled in each group over a 1-year timeframe. Peripheral blood samples will be obtained on each patient at time of enrollment. Healthy control patients will be undergoing elective hip replacement surgery for osteoarthritis, and a sample of bone will be taken from the proximal femur during surgery. Non-metastatic cancer patients will undergo bone marrow biopsy. Metastatic cancer patients will have a sample of their vertebral tumor removed during surgery. Bone tissue will be assayed using immunohistochemistry for MDSCs, osteoclast activity, DKK1, β-catenin, and CD4/CD8 T-lymphocytes. We hypothesize that the metastatic cancer patients will demonstrate higher numbers of MDSCs, higher osteoclastic activity, and lower numbers of CD4/CD8 T-cells than either the non-metastatic cancer patients or the cancer-free patients. Moreover, we postulate that the increased numbers of MDSCs in the metastatic patients will be associated with increased levels of DKK1 and β-catenin in the bone microenvironment. Peripheral blood will be assayed using flow cytometry. Again, relative numbers of MDSCs and CD4/CD8 T-lymphocytes will be quantified in the patients with skeletal metastases and the two control patient groups. A serum assay for DKK1 will quantify levels in the circulation. We hypothesize that the patients with metastatic tumors will have
higher numbers of circulating MDSCs, higher levels of DKK1, and lower numbers of circulating CD4/CD8 T-cells than either of the control groups.