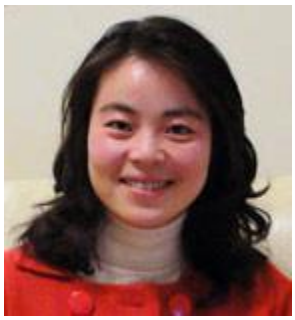
Pitt School of Dental Medicine Team Awarded $2 Million NCI Grant to Study How Cancer Spreads to Bone



With a $2 million, 5-year grant from the National Cancer Institute (NCI), part of the National Institutes of Health, McGowan Institute for Regenerative Medicine affiliated faculty member Hongjiao Ouyang, D.D.S., Ph.D., D.M.D., and researchers at the University of Pittsburgh School of Dental Medicine will examine the molecular mechanisms that allow certain cancers, particularly multiple myeloma, to spread to the bone. The project could lead to new interventions to prevent such metastases and perhaps slow down primary tumor growth.

About 30 percent of multiple myeloma patients are diagnosed after going to the dentist with jaw pain or suspicious lesions in the oral cavity, said the project's principal investigator Dr. Ouyang, associate professor of the Departments of Restorative Dentistry/Comprehensive Care and Oral Biology, and a member of the Center for Craniofacial Regeneration, Pitt School of Dental Medicine. Multiple myeloma is a cancer of plasma cells that begins in the bone marrow and is known for eating away the bone. Even with treatment, the bone lesions rarely heal.

"This bone destruction is a significant cause of pain and mortality in this disease," said Dr. Ouyang, an endodontist and bone biologist. "A better understanding of the molecular pathways that underlie this process could lead us to novel targets for treatment."

Bone marrow stromal cells (BMSCs) reside in the bone marrow and with appropriate stimulation can give rise to bone-forming cells called osteoblasts, fat cells, and other cells. In multiple myeloma, BMSCs produce growth factors and inflammatory proteins that boost tumor cells and activate osteoclasts, which are cells that break down bone while osteoblasts rebuild it as part of normal metabolism. In cancer, osteoclast activation makes holes in the bone that do not heal.

Dr. Ouyang's team has found that the BMSCs in multiple myeloma patients, unlike those in healthy people, produce much more X-box binding protein (XBP1s), a molecule that has been shown in other tissues to regulate the production of inflammatory proteins. Their lab experiments showed that inducing healthy cells to produce XBP1s leads to changes in the bone microenvironment that support growth of multiple myeloma cells and osteoclast formation. Conversely, knocking out XBP1 production in multiple myeloma patient BMSCs corrected the abnormalities.

For the newly funded project, the team will determine the molecular mechanisms of the stromal XBP1 signaling in altering the bone microenvironment to favor multiple myeloma growth and

bone destruction, as well as employ pharmacologic and genetic strategies to repress this molecule as a proof-of-concept for approaches to treat multiple myeloma bone disease.

“This could be helpful not only in treatment of multiple myeloma, but also in other cancers that spread to bone, such as breast, prostate, and lung cancer since BMSCs play a similar role in supporting tumor cell growth in these neoplastic diseases as well,” Dr. Ouyang said. “I am delighted that our research will benefit not only dental patients but also those affected by many other diseases.”

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