

Targeting MMPs to halt advanced metastatic breast cancer

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An upcoming G&D paper reveals how two specific matrix metalloproteinase (MMP) proteins contribute to bone metastasis in advanced breast cancer - lending important new insight into the design of clinically useful small molecule inhibitors.

The study was led by Dr. Yibin Kang in Princeton University in close collaboration with Dr. Joan Massagué at MSKCC and Dr. Michael Reiss at the Cancer Institute of New Jersey. It will be published online ahead of print at <u>www.genesdev.org/cgi/doi/10.1101/gad.1824809</u>.

"More than 70% of late stage breast cancer patients have skeletal complications," explains Dr. Yibin Kang. "It is important to uncover molecular mechanism of bone metastasis in order to come up with better treatments to reduce the pain and suffering from bone metastasis."

MMPs are a large class of related enzymatic proteins that degrade the extracellular matrix. Normal MMP activity is tightly regulated, and is necessary for a number of physiological processes, like tissue remodeling, angiogenesis, ovulation and wound healing. However, MMP dysregulation facilitates tumor metastasis.

MMP1 and ADAMTS1 are two different MMP family members that were previously identified in a genomic screen for breast cancer bone metastasis genes. Dr. Kang and colleagues now show how alterations in MMP1 and ADAMTS1 expression promote bone metastasis.



MMP1 and ADAMTS1 are upregulated in <u>breast cancer</u> cell lines with an enhanced ability to metastasize to bone. Dr. Kang and colleagues demonstrated that MMP1 and ADAMTS1 enzymatically cleave and release EGF-like growth factors from tumor cells to stimulate EGFR signaling in the bone-building osteoblasts. The researchers went on to show that such signaling reduces the production of OPG, a suppressor of the bone-resorbing osteoclasts, eventually leading to hyperactivity of osteoclasts, bone destruction and subsequent expansion of bone metastasis.

Thus, this paper supports a rationale for the therapeutic targeting of MMP1 and ADAMTS1, and suggests that inhibition of EGFR signaling in bone stromal cells to block osteoclast activity may represent a viable method of mitigating bone complications in advanced metastatic breast cancers.

Source: Cold Spring Harbor Laboratory (<u>news</u> : <u>web</u>)

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