

OSTEOSCOOP

News on current events in osteoporosis and rheumatology

GM-CSF stimulates osteoclastogenesis: therapeutic caution is required

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Patients with a variety of tumors, including those with breast cancer, are often treated with granulocyte–monocyte colony stimulating factor (GM-CSF), a cytokine that increases white cell counts. GM-CSF stimulates the proliferation and differentiation of hematopoietic precursors, thereby replenishing blood cells ravaged by chemotherapy.

In a recent study, Park et al. [1] raise cautions about using GM-CSF in patients with breast cancer. In animal models, they show that GM-CSF promotes breast cancer metastases that destroy bone. They report that human breast cancer cells that are metastatic to bone have increased NF-kappa B signaling that results in the production of high levels of GM-CSF. GM-CSF in turn induces osteoclast formation and bone destruction. Blocking GM-CSF production or activity decreased osteoclasts growth and osteoclastic bone destruction in an animal model of breast cancer. Other NF- kappa B–regulated genes that induce osteoclast formation, such as genes encoding IL-8 or IL-6, were also expressed by the breast cancer cells.

Since GM-CSF can increase osteoclast formation, the authors asked whether GM-CSF expression might be driving metastasis. They confirmed that GM-CSF induced osteoclast formation in human bone marrow cultures and that transfecting breast cancer cells with a super-repressor of NF-kappa B decreased the capacity of these breast cancer cells to metastasize to bone. Importantly, they showed that transfecting breast cancer cell lines that normally do not metastasize to bone with a GM-CSF expression vector increased their bone-metastatic potential. It is likely that other factors also produced by breast cancer cells, such as RANKL, IL-8 or PTHrP, are providing the differentiation stimulus required for GM-CSF to increase osteoclast formation and bone metastasis [2].

Further studies should help to determine whether administering GM-CSF to breast cancer patients puts them at risk. These new findings suggest that GM-CSF should be added to the list of factors involved in breast cancer bone metastasis and that GM-CSF may represent a new therapeutic target for such metastasis.

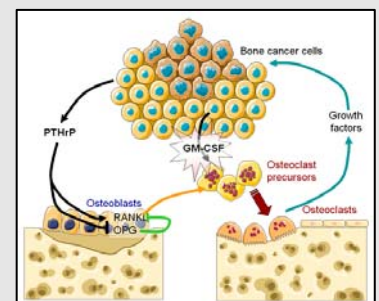
1. Park BK et al. *Nature Med.* 2007;13:62-69.
2. Roodman GD. *Nature Med.* 2007;13:25-26.

GM-CSF stimulates osteoclastogenesis

GM-CSF may be secreted by cancer cells which are metastatic to bone or administered as a therapy in order to increase white cell count.

GM-CSF recruits osteoclast precursors and differentiated them in mature resorbing osteoclast. This effect may be potentiated by PTHrP, also secreted by cancer cells, which increases RANK ligand and decreases osteoprotegerin.

Bone resorption contributes to release growth factors from the extracellular matrix, which enhance tumor growth.



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