CSF-1 blockade impairs breast cancer osteoclastogenic potential in co-culture systems

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A B S T R A C T

Metastatic bone disease has a major impact on the morbidity and mortality of breast cancer patients, and studies on bone metastasis biology have led to the development of the most widely used drugs for bone metastases treatment: zoledronate (Zol) and denosumab (Den). The aim of the present study was to assess the effect of soluble mediators produced by breast cancer cells on human osteoclast maturation in a co-culture model. We also tested the ability of zoledronate, denosumab and 5H4, an antibody directed against CSF-1, to interfere with the osteoclastogenic potential of breast cancer. The study was performed on the triple negative cell line MDA-MB-231 and on human osteoclasts obtained from the differentiation of peripheral blood monocytes of a healthy volunteer. Osteoclastogenesis was evaluated by TRAP assay after 14 days of differentiation with 10% MDA-MB-231-conditioned media or with CSF-1 and RANKL. Den, Zol and 5H4 were administered after 7 days of differentiation. MDA-MB-231-conditioned media doubled the differentiation of monocytes into osteoclasts. MDA-MB-231 secreted CSF-1, especially when cells were cultured to confluence. Induced osteoclasts were sensitive to bone-targeted drugs: Den and 5H4 blocked osteoclast differentiation and survival, while Zol induced osteoclast apoptosis. Osteoclasts differentiated by breast cancer cells were less sensitive to Zol than those induced by differentiation factors, whereas sensitivity to Den was similar. Conversely, breast cancer-induced osteoclast activation resulted in a higher sensitivity to 5H4. A significant increase in CSF-1 secretion was observed in osteoclast precursors after treatment with the highest concentration of Den. Further research is ongoing to evaluate the efficacy of 5H4 combination with Den.