Breast cancer cells stimulate osteoclastogenesis

Vanessa Nicolin, Roberta Bortul, Renato Bareggi, Paola Narducci

Department of Biomedicine, University of Trieste, Italy

Bone metastatic breast cancer is a serious clinical problem resulting in hypercalcemia, bone fragility and pain, an understanding of the underlying molecular mechanism would be highly valuable. The invasion of bone tissue by neoplastic cells usually very rapidly affects the balance between bone apposition and bone resorption. In order to elucidate a mechanism for cancer-induced osteoclastogenesis, cells from human breast cancer cell line, MCF-7 were directly co-cultured with murine monocytes RAW 264,7 type CRL 2278. The breast cancer cells in this coculture system secrete factors that act in a paracrine fashion to active osteoclasts: MCF-7 induced differentiation of multinucleated cells by membrane-bound and soluble receptor activator of NF-kB ligand (RANKL) as shown by ELISA, Western blot analysis, transmission electron microscopy (TEM) and immunocytochemistry. RANKL is counteracted by Osteoprotegerin (OPG), which is a soluble decoy receptor for RANKL and blocks ligand binding to RANK, thus preventing the signalling required for osteoclast differentiation and activation. In the present study we observed that breast cancer cells expressed RANKL as two isoforms identified as transmembrane (Tm-isoform) and extracellular (Ex-isoform).The neutralization of RANKL by OPG resulted a complete inhibition of osteoclastic differentiation demonstrating that RANKL has an important role in the control of metastatic breast cancer behaviour. Our present finding indicates that the cells that were generated by coculture, in which we use breast cancer cells, were really osteoclasts and that this is due to the RANKL production. The implications are particularly noteworthy for the potential applications of drug that selectly regulate the expression of RANK-ligand isoform in the treatment of malignancies with bone osteolytic lesions.

References

Nicolin V et al. (2006) J.Mol Hist. 17, 171-177.
Nicolin V et al. (2008) Acta Histochemica 110, 388-396.
Narducci P et al. (2010) Acta Histochemica (in press).

Key words
Breast cancer cells, coculture, osteoclastogenesis, RANK/RANKL/OPG