

OSTEOSCOOP

News on current events in osteoporosis and rheumatology

RANK mediates tumor-infiltrating regulatory T-cells stimulation of mammary cancer metastasis

N°189 - June 2011

Receptor activator of nuclear factor- κ B (RANK)-ligand (RANKL) signaling is associated with osteoclast differentiation and bone resorption. Inhibition of this pathway by specific RANKL antibodies is an effective way to reduce bone metastases. Recent studies showed that this pathway was activated in prostate or breast cancer, although its precise mechanism is unknown. The objective of this study [1] was to investigate the source and the role of RANKL and the RANK-RANKL signaling in breast cancer pulmonary metastasis.

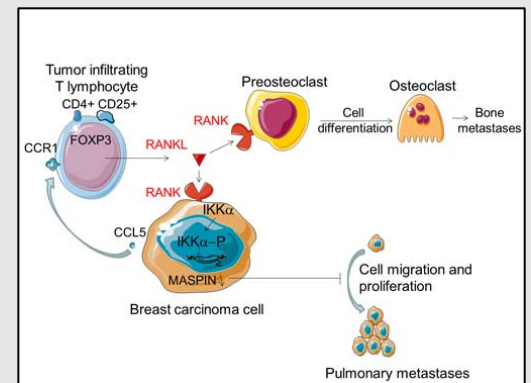
Indeed, exogenous RANKL (RANK ligand) in mammary carcinoma cells activates pulmonary metastasis. On the contrary, the silencing of RANK (RANKL receptor) reduces pulmonary metastasis. This prometastatic effect is mediated by reduced expression of metastasis inhibitor factor MASPIN, a protease inhibitor also known as SerpinB5, in breast carcinoma cancer cells. Metastatic spread of carcinoma cells also required CD4+ CD25+ regulatory T cells, in mouse and human breast cancers. These cells are the main producers of RANKL in breast tumors.

These results are consistent with the adverse impact of tumor-infiltrating regulatory T cells on human breast cancer prognosis and suggest that the targeting of RANKL-RANK can be used in conjunction with the therapeutic elimination of primary breast tumors to prevent recurrent metastatic disease.

1. Tan et al. *Nature*. 2011;470:548-553.

RANK mediates tumor-infiltrating regulatory T-cell stimulation of mammary cancer metastasis

The RANK (receptor of nuclear factor- κ B) – RANKL (Ligand) signaling is well known to promote osteoclast differentiation. Inhibition of signaling using a humanized RANKL antibody is an effective inhibitor of breast cancer bone metastasis. This signaling is also involved in the breast cancer pulmonary metastasis. Activation of breast carcinoma cells RANK by RANKL leads to nuclear localization and phosphorylation of inhibitor of nuclear factor- κ B kinase α (IKK- α). This transcription factor reduces the expression of metastasis inhibitor factor Maspin. Low levels of MASPIN induce pulmonary metastasis formation. The production of RANKL in tumor is mainly due to CD4+ CD25+ FOXP3+ regulatory T lymphocytes. Infiltration of such lymphocytes into tumor could be mediated by cancer cell production of CCL5 and its interaction with T lymphocyte receptor CCR1.



PROTELOS[®]
Treatment of postmenopausal osteoporosis to reduce the risk of hip and vertebral fractures

