Researchers propose biomarkers to select breast cancer patients who could benefit from denosumab treatment

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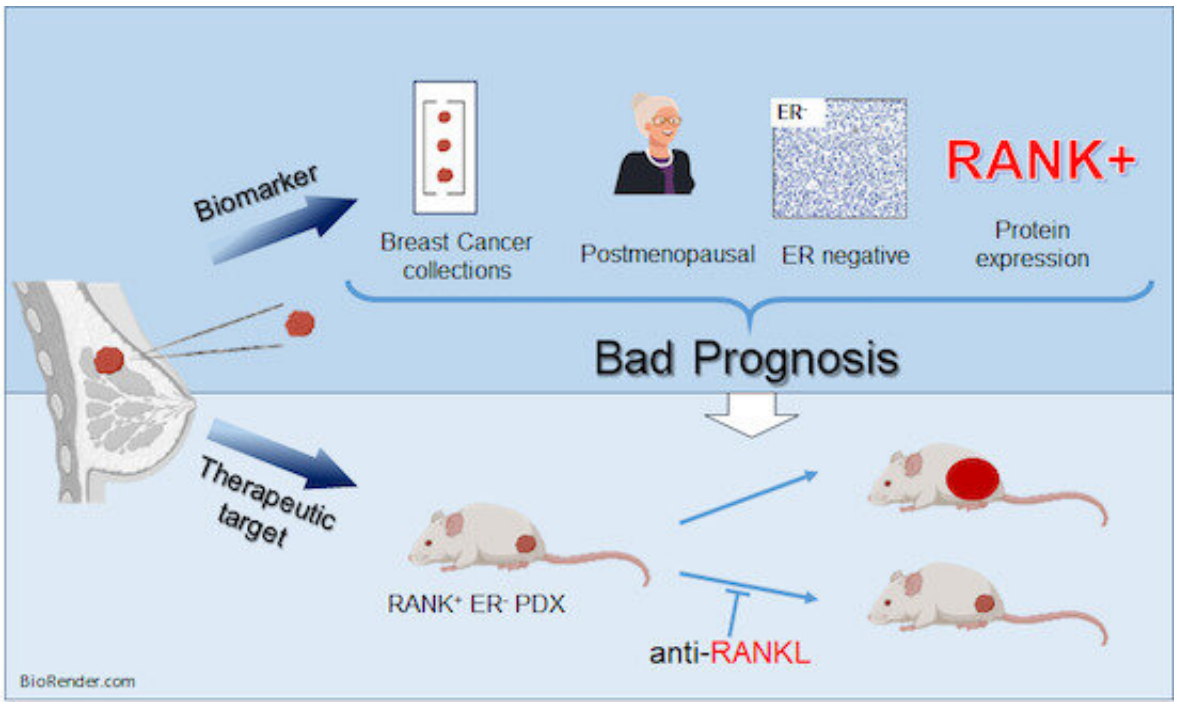

Graphical abstract. Credit: *EMBO Molecular Medicine* (2023). DOI: 10.15252/emmm.202216715

The drug denosumab is currently used to treat osteoporosis and bone metastases. For more than a decade, its potential therapeutic benefit in the treatment of breast cancer has also been studied. However, due to conflicting clinical data, the survival benefit in breast cancer patients is

unclear.

With the aim of selecting patients who could benefit from this drug, researchers from the Spanish National Cancer Research Center (CNIO) and the Bellvitge Biomedical Research Institute (IDIBELL), led by Eva González-Suárez, have analyzed the expression of the RANK protein and its RANKL ligand in more than 2,000 breast tumors, including 777 without hormone receptor expression, from four independent cohorts. The study is published in the journal *EMBO Molecular Medicine*.

Their results show that RANK protein expression is more frequent in tumors without hormone receptors, where it was associated with poor prognosis and poor response to chemotherapy. In addition, the researchers observed increased activation of the RANK pathway in breast tumors after menopause, suggesting that the use of the inhibitor denosumab, added to standard of care, may be of greater therapeutic value in postmenopausal patients with hormone receptor-negative breast tumors and RANK protein expression.

Tumors without hormone receptors, where the cancer cells lack estrogen and progesterone receptors, have a worse prognosis and limited treatment options. "Given the heterogeneity of the group of hormone receptor–negative breast tumors, it is essential to have biomarkers that better distinguish the prognosis of these patients, especially if these markers allow us to choose the most appropriate treatment," says Eva González-Suárez, head of the Transformation and Metastasis Group at the CNIO.

"The reliability of the results is high," she adds. "They suggest that there is a group of patients who could benefit from treatment with denosumab and reactivate the option of starting breast cancer trials by selecting patients."

The next step would therefore be to "design a clinical trial in patients with hormone-receptor negative tumors expressing the RANK receptor and in pre- and post-menopausal patients."

RANK in different breast tumors

The RANK protein is located in the cell membrane and when it binds to RANKL, it sends key signals that allow the mammary gland to develop properly and produce milk. In previous studies, Gonzalez-Suarez and colleagues showed that inhibiting RANKL with drugs such as denosumab could be a way to prevent the disease.

Gonzalez-Suarez and her team then demonstrated that pharmacological inhibition of the RANK/RANKL pathway reduced recurrence and metastasis in mouse models of breast cancer. Subsequent steps have focused on further understanding this relationship between RANK and the different types of human breast tumors, given the great heterogeneity of the disease in patients.

The RANK protein was initially described for its role in immunity. It was later found to play a key role in bone metabolism: activation of the RANK pathway is essential for the differentiation and functionality of osteoclasts, the cells responsible for bone resorption, which is why the first therapeutic indication for denosumab is osteoporosis and bone metastasis. "This is the best known and most therapeutically exploited role of RANK," explains González-Suárez.

"Subsequently, in my group, we have shown that it is also important in the development of the mammary gland: we observed that it acts as a mediator of progesterone, which is essential for its ability to produce milk, but also in the development of breast cancer. Let's say that in order to form a tumor, breast epithelial cells have to divide, but if you block RANK pathway that is the main mediator of that division, you can

prevent breast cancer."

More than 2,000 samples from four cohorts

In this new study, Marina Ciscar and Eva M. Trinidad, co-first authors of the study, teamed up to determine the therapeutic value of the pathway in breast cancer. Ciscar and other members of González-Suárez's team analyzed these proteins in more than 2,000 breast tumor samples from four older cohorts, mainly from Emad Rakha's team at the University of Nottingham, where they have been following patients for two decades, and two Spanish cohorts, from the Bellvitge Biomedical Research Institute (IDIBELL) and the CNIO.

Ciscar and her collaborators found that 40% of hormone-negative tumors expressed the RANK receptor, and that this expression was associated with worse prognosis and survival.

Eva M. Trinidad used experimental mouse models in which she implanted a small fragment of human tumors in the same organ of origin. In these models, RANKL inhibition reduced tumor cell proliferation and plasticity, regulated tumor immunity and metabolism, and improved response to chemotherapy. The researchers concluded that the RANK pathway could serve as both a biomarker and a therapeutic target.

"This research follows on from previous observations where we had already seen that the receptor is more frequently expressed in tumors without hormone receptors. In this work, the analysis is much more powerful and has allowed us to conclude that within tumors that do not have hormone receptors, the presence or absence of the RANK receptor is associated with the prognosis of the disease," explains González-Suárez.

Two large phase III clinical trials with the primary aim of preventing bone metastases also looked at whether denosumab could increase overall survival in women. The results were contradictory, but the fact is that "none of the trials looked at receptor expression in patients: when they say that denosumab does not improve survival, they have not looked at whether the tumor expresses the receptor or not, which is a fundamental point. As the results of one of the trials were negative, the door was somewhat closed to trials of denosumab in breast cancer. I think that this study reactivates the possibility of doing them again, with patient selection," the researcher concludes.

More information: Marina Ciscar et al, RANK is a poor prognosis marker and a therapeutic target in ER -negative postmenopausal breast cancer, *EMBO Molecular Medicine* (2023). DOI: 10.15252/emmm.202216715

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