

Radical increase in the effectiveness of breast cancer immunotherapy

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A study published in the journal *Nature Cancer*, carried out within the Cancer Program at the Hospital del Mar Medical Research Institute (IMIM-Hospital del Mar) by the Cancer Stem Cells and Metastasis Dynamics Laboratory, led by Dr. Toni Celià-Terrassa, and the Laboratory of Molecular Cancer Therapy, coordinated by Dr. Joan Albanell, with the participation of international centers, has discovered an approach that radically increases the success of immunotherapy in one of the most aggressive types of tumors, triple-negative breast cancer. This subtype, although accounting for only 15% of cases, is one of the most rapidly progressing and affects younger patients. In this work, researchers found that tumor stem cells are the main cause of immunotherapy resistance in this subtype of breast cancer. The reason is that these cells are invisible to the immune system, making immunotherapy ineffective. In addition, the study offers a promising solution to this situation by using a new therapeutic approach in preclinical models that makes cancer stem cells visible to the immune system so that it can then eliminate the tumor.

This subpopulation of more aggressive cells may represent between 5% and 50% of the entire tumor population in triple-negative breast cancer. They have low levels of ligand-dependent corepressor (LCOR) factor, which plays a key but previously unknown role in allowing cells to present antigens on their surface, molecules that enable the immune system to differentiate [normal cells](#) from tumor cells and attack the latter. Consequently, in the case of tumor stem cells, the low presence of this LCOR factor makes them invisible to the body's defenses. As a result, these cells are resistant to breast cancer [immunotherapy](#), which has a relatively low success rate in current clinical practice.

A mechanism that provokes treatment resistance

This ability of tumor stem cells to remain invisible to the immune system allows them to withstand immunotherapy treatment. As Dr. Toni Celià-

Terrassa explains, "We have seen how, despite immunotherapy treatment, these cells survive and have the ability to generate resistance, which is linked to their ability to hide from the immune system, allowing them to evade immunotherapy."

Using mouse models, the researchers have demonstrated how this situation is reversed when the LCOR gene is activated in this type of cell, setting in motion the machinery that allows the immune system to detect the tumor. "It involves reconfiguring the tumor to make it completely visible and, therefore, sensitive to immunotherapy, transforming it from invisible to visible," says Iván Pérez-Núñez, a pre-doctoral researcher in the Cancer Stem Cells and Metastasis Dynamics Laboratory and first author of the study. The researchers were able to see how, by combining this approach with immunotherapy, the treatment response rate was total, and all tumors were eliminated, curing the mice in the long term. This prevents both the recurrence of cancer and the generation of resistance.

Pioneering study on the use of messenger-RNA therapy in cancer and immunotherapy

Inspired by the technology used in the design of messenger-RNA vaccines for COVID-19, the researchers decided to use a similar strategy to transport and deliver LCOR gene RNA into tumor cells and trigger its function. Biological nanovesicles, small bag-like structures formed in the cells, were developed to carry this information and were shown to do so successfully, preventing the tumor stem cells from remaining invisible.

"What we are doing is making the immune system see the tumor cell better. Unlike healthy cells, malignant cells have a much higher load of recognized 'foreign' antigens, which are not inherent to the [immune system](#). In this way, the body's natural defenses will recognize, attack

and eliminate the malignant cells," explains Dr. Celià-Terrassa. In this sense, he points out that "We have discovered how to make this type of breast cancer respond to immunotherapy in [preclinical models](#), making these cells visible thanks to the use of the antigen-presenting mechanism, thereby boosting the immunotherapy response and its efficiency."

This strategy may be applicable to other types of breast cancer tumors and other tumor types, although safety studies and clinical trials in humans are needed first. Even so, according to Dr. Joan Albanell, co-leader of the study, director of the Cancer Research Program at IMIM-Hospital del Mar and head of the Oncology Department at Hospital del Mar, this approach does open up new possibilities. "What is important is that the experimental results demonstrate an unprecedented sensitization of triple-negative breast cancer to immunotherapy, making resistant tumors virtually curable," says Dr. Albanell, also a professor at the UPF. "This unequivocally motivates us to investigate therapeutic strategies that may culminate in clinical trials, and to explore whether it could be applicable to other tumors," he concludes.

The use of LCOR in combination with immunotherapy has generated a patent and a spin-off company will be created to develop this. "The project led by Dr. Celià-Terrassa and Dr. Albanell is a paradigmatic example of research in immune therapies that will be boosted in the near future by the new Immuno-oncology Division that we are creating at the IMIM," explains Dr. Joaquín Arribas, director of the IMIM-Hospital del Mar and author of the study.

Immunotherapy in cancer and breast cancer

Immunotherapy is one of the most promising treatments for eradicating tumors and curing cancer. Unfortunately, for breast cancers it is only approved in the [triple-negative breast cancer](#) subtype, where the outcomes are still far from what is expected from immunotherapy.

Making immunotherapy work in breast cancer would be a great therapeutic opportunity for the breast cancer population, making it a very good option for more advanced and metastatic cases. It should be remembered that metastatic breast [cancer](#), despite significant and continuous advances, is still not curable in the majority of patients.

More information: Joan Albanell, LCOR mediates interferon-independent tumor immunogenicity and responsiveness to immune-checkpoint blockade in triple-negative breast cancer, *Nature Cancer* (2022). DOI: [10.1038/s43018-022-00339-4](https://doi.org/10.1038/s43018-022-00339-4).
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