Hospital del Mar Research Institute Barcelona

PRESS RELEASE

Pathway discovered to make the most common breast cancer tumor responsive to immunotherapy

- ***A study from the Hospital del Mar Research Institute, published in The Journal of Clinical Investigation, indicates that the high expression of the estrogen receptor is the main factor preventing the most common type of breast cancer, luminal breast cancer, from responding to immunotherapy.***

- ***The high presence of the estrogen receptor sequesters the LCOR molecule, whose action on tumor cells is necessary to make tumors visible to the immune system. In experimental models, the researchers found that combining immunotherapy with endocrine therapy allows LCOR to function and the immune system to attack the tumor.***

- ***At the same time, they have generated a modified version of the LCOR molecule that sensitizes tumors to immunotherapy, including those with hormone receptors. The next goal is to study this molecule combined with immunotherapy in clinical trials.***

Barcelona, December 4, 2025 – A study led by researchers at the Hospital del Mar Research Institute advances one of the most significant milestones in breast cancer treatment, making immunotherapy effective against the most common tumor type, estrogen receptor-positive or luminal breast cancer. This subtype accounts for 70% of breast cancer cases, and despite effective treatments, it causes the highest mortality in total cases. Additionally, immunotherapy is not effective or approved because it shows no immune system response in these tumors, except in a minority subgroup that, precisely, has low estrogen receptor levels. The work is published by The Journal of Clinical Investigation and led by Dr. Toni Celià-Terrassa's team from the Cancer Stem Cells and Metastasis Dynamics Laboratory at the Hospital del Mar Research Institute. The study is supported by Ausonia through the Spanish Association Against Cancer.

The study highlights the importance of the **estrogen receptor** in the tumor's strategy to evade immune system action. By analyzing public data from various clinical trials, the researchers found that this factor limits immune system infiltration and prevents immunotherapy from being effective. In contrast, inhibiting the estrogen receptor allows the activation of LCOR and interferon signals, both factors related to antigen presentation mechanisms on the cell surface, making the tumor cell visible to the immune system.

The next step was to generate a preclinical model in animal models, which confirmed this tumor protection mechanism. They also found that the **LCOR molecule**, which in other preclinical studies in triple-negative breast cancer increased the effectiveness of immunotherapy, was 'sequestered' by the estrogen receptor and could not perform this function. "***The estrogen receptor sequesters LCOR and prevents it from activating the antigen-presenting machinery, conditioning its function and not allowing the tumor to become 'visible'***," explains Dr. Toni Celià-Terrassa, coordinator of the Cancer Stem Cells and Metastasis Dynamics Laboratory at the Hospital del Mar Research Institute.

To address this effect, the research team used two strategies in the preclinical setting. First, they **combined LCOR and immunotherapy with hormonal inhibitors,** or endocrine therapy, already used to treat this type of cancer. Second, they created a modified version of LCOR (LSKAA) that prevents sequestration by the estrogen receptor. ***"Under normal conditions, estrogen signaling is prevalent in this type of tumor and prevents LCOR from acting. If we manage to break this signaling with antiestrogen therapy, LCOR activates antigen presentation and opens the path for immunotherapy,"*** adds José Ángel Palomeque, researcher at the Hospital del Mar Research Institute. This modified LCOR escapes the estrogen receptor's action and enhances antigen presentation, necessary for immune attack.

In this regard, the RNA therapy generation laboratory at the Hospital del Mar Research Institute uses this technology to create modified LCOR therapies that do not interact with the estrogen receptor in combination with immunotherapy. Additionally, the recently established spin-off VIOLET Pharmaceuticals focuses on these types of therapies.

Dr. Joan Albanell, head of the Medical Oncology Service at the Hospital del Mar and director of the Cancer Research Program at the Hospital del Mar Research Institute, states that "***this study opens the door to a new strategy to sensitize this subtype of breast cancer to immunotherapy."*** The goal is to work towards "***turning this modified LCOR into a therapy that can be investigated in upcoming clinical trials, especially for patients with tumors that present estrogen receptors, which currently limit the effectiveness of immunotherapy,***" he explains.

Reference article

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More information

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