

Natural killer cells predict the treatment response of patients with the most aggressive breast cancer

- **Researchers from the Hospital del Mar and Hospital del Mar Medical Research Institute (IMIM) have led a study verifying the importance of the presence of a specific type of lymphocyte in the success of anti-tumour treatments in patients with HER2-positive breast cancer.**
- **This is the first time that the role of these immune system cells in treatment response has been verified with patient samples. The role HLA molecules play in obtaining good results has also been determined.**
- **This work leads the way to finding new methods for reinforcing both existing treatments and those in a trial phase, including the possibility of transplanting NK cells from healthy patients into cancer sufferers. The study has been published in the journal *Clinical Cancer Research***

Barcelona, February 22, 2019. - Patients with one of the most aggressive types of breast cancer, **HER2 positive**, have a greater chance of a complete treatment response if the tumours contain high levels of a particular type of lymphocyte, the so-called Natural Killer cells (NK). This is the first time that this relationship has been seen in the tumours of breast cancer patients, in an important step towards finding markers that indicate the drug-response level of patients. At the same time, this finding, published in the journal *Clinical Cancer Research*, indicates new ways of reinforcing existing tumour-removal treatments, as well as those in a trial phase, and leads the way to discovering methods for transplanting this type of cell in combination with monoclonal antibodies.

The study was headed up by researchers from the Hospital del Mar, Hospital del Mar Medical Research Institute (IMIM), and Pompeu Fabra University, in collaboration with professionals from the Fundación Jiménez Díaz in Madrid and Hospital Clínic in Valencia, as well as the Institute for Research in Biomedicine (IRB) in Barcelona. The project used samples from more than a hundred patients with HER2-positive breast cancer

The importance of NK cell levels to the tumour

The results of the study enabled the researchers to conclude that patients with high levels of NK cells in their tumours, who had been treated prior to surgery with monoclonal antibodies against HER2, were more likely to achieve a complete disease-response to the treatment. In contrast, in cases with low levels of NKs, complete remission was rarely achieved. This relationship between NK lymphocytes and treatment response indicates that the immune system is possibly involved in the anti-tumour action of these drugs. **"The monoclonal antibody acts as a bridge between the HER2-positive tumour cell and the NK cell, which, through this bond, perforates the tumour cell, introducing cytotoxic material and destroying it"**, explains Dr. Joan Albanell, head of the Medical Oncology Service at the Hospital del Mar, CIBERONC researcher, and director of the IMIM Cancer Research Programme, last author of the study together with Dr. Miguel López-Botet, head of the Immunology Service at the Hospital del Mar and coordinator of the IMIM's Immunity and Infection Research Group, both lecturers at Pompeu Fabra University.

"What we have shown is that there is an association between the presence of NK lymphocytes and the complete elimination of tumours during treatment with HER2-specific therapeutic antibodies. In some tumours no NK lymphocytes are detected, and, in these cases, treatment responses are partial or non-existent", emphasises first author of the study, Dr. Aura Muntasell, a researcher in the IMIM's Immunity and Infections research group. Until now, evidence of this interaction had only been found in *in vitro* trials and experimental preclinical models. To arrive at these conclusions, the researchers developed a technique that enabled them to visualise and quantify the number of NK cells in tumours.

New lines of research

The researchers are currently working on validating the predictive value of NK cells in samples from breast cancer patients treated with anti-HER2 therapies in clinical trials. Research is focused on reinforcing the action of anti-tumour treatments in patients with HER2-positive breast cancer, and new monoclonal antibodies capable of 'recruiting' this type of cell to attack the tumour. They are also looking at the possibility of transplanting NK cells from healthy patients into cancer sufferers, or performing cell therapy with these lymphocytes to obtain a better response. ***"From the immunological point of view, this study indirectly indicates that NK cells may play an active role in the anti-tumour effect of the treatment. This encourages us to continue investing in strategies to get more NK cells into the tumour and boost their activity to increase the clinical efficacy of anti-HER2 antibody treatments."***, notes Dr. Muntasell.

"We are designing a clinical trial to test the viability of NK cell transplants in women with HER2-positive breast cancer, in combination with monoclonal antibodies. This clinical trial is the result of years of collaborative work led by Dr. Ignacio Melero from the Centre for Applied Medical Research (CIMA), in collaboration with researchers from the VHIO and Puerta de Hierro Hospital in Madrid, with funding from the Spanish Association Against Cancer (AECC)", explains Dr. Albanell.

The role of HLA class I molecules

Another aspect described in the paper is the relationship between the **HLA class I molecule** expression level in tumour cells (molecules expressed on the surface of the tumour and unique to each individual), and the risk of relapse. These molecules allow other immune system lymphocytes (T lymphocytes) to recognise tumours and participate in their elimination. Some tumours totally or partially silence the expression of HLA class I molecules to avoid being recognised by T lymphocytes. This study indicates that tumours which have silenced the expression of HLA class I molecules have a higher risk of relapse in the long term. Dr. Albanell Com explains, ***"The combination of HLA class I expression and NK cells may improve our ability to predict long-term relapse and provide new treatment approaches"***.

HER2-positive breast cancer

Each year, nearly 28,000 cases of breast cancer are diagnosed in Spain (according to Spanish Society of Medical Oncology (SEOM) data), of which 4,600 are in Catalonia (according to the Department of Health). Of these, between 15% and 20% are HER2-positive type. This subtype is characterised by the presence of the HER2 oncogene in tumour cells, associated with aggressive clinical evolution. Thanks to the development of specific treatments, the poor prognosis has been reversed in all phases of the disease. There are still, however, important challenges related to improving personalised treatment, knowledge of *de novo* and acquired resistance mechanisms, and developing new strategies to continue making steps towards a cure.

Reference article

NK cell infiltrates and HLA class I expression in primary HER2+ breast cancer predict and uncouple pathological response and disease-free survival.

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