Press Release

New tool to boost cancer immunotherapy effects

- ***The genetic modification of the Natural Killer (NK) cells, lymphocytes forming part of the body's immune system, would make it possible to retain their capacity of eliminating tumour cells in solid tumours***
- ***Some types of tumours secrete two molecules, TGF-β and Activin A, which supress the capacity of NK cells to attack them***
- ***A team of researchers from the Hospital del Mar Research Institute, the Universitat Autònoma de Barcelona and the Pompeu Fabra University has developed a new tool that allows modifying these NK cells to make them immune to the tumour's defense mechanism***

Barcelona, March 24th, 2025. – Among other functions, the **NK cells** (*Natural Killers*, a type of lymphocyte forming part of the immune system) have the capacity to detect and eliminate cancer cells. But in some cases they cannot overcome the tumour's defense mechanism and the cancer grows. Now, a study published in *Nature Immunology*, with the involvement of the Hospital del Mar Research Institute, the Universitat Autònoma de Barcelona and the Pompeu Fabra University, proposes a **new approach** to strengthen NK cells in their fight agaist tumour cells.

The study, which included the collaboration of researchers from the Karolinska Institutet in Sweden, the German firm Miltenyi, and the Dutch firm Glycostem Therapeutics, was developed under the context of a European network. It also included the involvement of researchers from the Hospital Clínic-IDIBAPS, and from the CIBER Cancer Unit (CIBERONC), the CIBER Hepatic and Digestive Disorders Unit (CIBERehd), and the CIBER Infectious Diseases Unit (CIBERinfec). To strengthen the capacity of NK lymphocytes to eliminate tumours researchers **used CRISPR/Cas9**, a genetic editing tool, to eliminate a gene from these cells and make them resistant to two molecules that produce tumour cells.

The goal of the study was to confirm whether modified NK cells had the capacity to overcome the negative effects of the **TGF-β and Activin A molecules** in preclinical models of HER2 positive breast cancer tumour cells and metastatic colorectal cancer cells. The majority of solid tumours contain an abundance of both molecules to protect themselves against attacks from the immune system. The results, both in vitro and in mice models, demonstrate that the genetically modified NK cells are capable of reaching the tumours, penetrating and destroying them, i.e., break their protective barrier. ***"When we compare genetically modified cells with non-modified cells, the first have a greater capacity to control the growth of in vivo tumours, both alone and when combined with other treatments and therapies being used, such as for example specific HER2 antibodies"***, explains Dr Aura Muntasell, researcher from the Immunity and Infection Research Group of the Hospital del Mar Research Institute and lecturer in the Department of Cell Biology, Physiology and Immunology of the Universitat Autònoma de Barcelona.

Modifying the *SMAD4* gene

To achieve these effects, researchers deactivated a specific gene, the ***SMAD4***, involved in the signalling of TGF-β and Activin A. ***"To achieve this disactivation, the NK cells were transitorally exposed to the CRISPR/cas9 system, programmed with a guide so that they could head specifically towards the SMAD4, edit it and disappear"***, explains Marc Güell, ICREA research lecturer and head of the Synbio Lab of the Pompeu Fabra University (UPF).

"By eliminating the SMAD4 we make these cells resistant to the TGF-β's inhibition but we continue to make use of the rest of the molecule's signalling to have them

acquire a greater capacity to reach tumours and penetrate them", adds Dr Muntasell. The study now published allows demonstrating the safety and efficiency of this approach. In collaboration with other institutions, it was also possible to verify that using it with other treatments under development that are based on the NK cells enables boosting its effect. ***"This strategy is also aplicable to NK cells generated through different protocols, including those expressing chimeric antigen receptors (CAR), which allows recognising specific antigens found in cancer cells. In addition, it is promising for several clinical indications, since the TGF-β supresses the immune response in multiple types of cancer"***, points out Dr Anna Rea, first autor of the article on the research conducted in her PhD thesis project at the UPF.

So far, treatments based on NK lymphocytes have been successful in hematological tumours, but have not achieved the same level of effectiveness in solid tumours. **"These genetically modified NK cells offer a great treatment opportunity for patients with solid tumours that are currently resistant to immunotherapy"**, explains Dr Clara Montagut, researcher at the Hospital de Mar Research Institute and head of the Digestive Oncology section in the Hospital del Mar Medical Oncology Service.

Dr Muntasell and Dr Montagut are precisely the two researchers leading a project that has received one of the independent research grants from the Instituto de Salud Carlos III. The grant will go towards developing a phase I clinical trial, the first of its kind, to prove the safety and tolerability of CRISP/Cas9-modified NK cells in combination with other treatments, in patients with refractory colon and rectal cancer.

Reference article

Rea, A., Santana-Hernández, S., Villanueva, J. *et al.* Enhancing human NK cell antitumor function by knocking out *SMAD4* to counteract TGFβ and activin A suppression. *Nat Immunol* (2025). https://www.nature.com/articles/s41590-025-02103-z

More information

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