Press Release

Tumor Killer in Top Form

Freiburg immunologists discover a new method for training immune cells to attack cancer cells

The signal to kill: Prof. Dr. **Wolfgang Schamel** and his team at the Institute of Biology III and the Cluster of Excellence BIOSS Centre for Biological Signalling Studies of the University of Freiburg have found a signal that causes the T cells of the immune system to attack cancer cells much more effectively. The researchers use antibodies to activate a rare type of T cells in the blood, the γδ T cell, in a new way. The γδ T cells recognise metabolic products, that are produced by cancer cells, and attack these tumor cells. “The γδ T cells in the petri dish killed tumor cells twelve times more effectively with our method than with previous activation methods,” explains Schamel. In the future, this method could be used to stimulate the immune system of cancer patients to fight tumors more effectively.

Immune therapies are designed to strengthen the cancer patient’s natural defense by activating T cells. γδ T cells are particularly interesting for such therapies because they kill off a broader spectrum of different types of cancer than the much more common αβ T cells. αβ T cells respond to tumor antigens, which differ from cancer type to cancer type and often also from patient to patient. γδ T cells, on the other hand, respond to changes in cellular metabolism that are common to many types of cancer. This renders the γδ T cells effective cancer killers for many different types of cancer. They multiply when activated and destroy the affected tumor cells. But in cancer patients they are often not active enough to gain the upper hand over the cancer.

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Both γδ and αβ T cells are equipped with a T cell receptor, which recognises substances on cancer cells that give them the signal to attack. If one of these substances binds to the receptor, the receptor changes in structure. This so-called conformational change transmits the signal to the inside of the T cell. This signal was the focus of detailed investigation in the EU-funded project SYBILLA, "Systems Biology of T-Cell Activation in Health and Disease." With previous methods, scientists were able to activate γδ T cells, but they did not observe any conformational changes. In the current study, the findings of which have now been published in the journal *Cell Reports*, Schamel succeeded together with Prof. Dr. **Paul Fisch** from the Department of Pathology of the University Clinics Freiburg in bringing about this change in the conformation of the receptor for the first time ever with the help of an antibody. In this way, Schamel and his team managed to enhance the anti-tumor effect of the cells in cooperation with Prof. Dr. **Dieter Kabelitz** and PD Dr. **Daniela Wesch** from the Institute of Immunology of the Schleswig Holstein University Medical Center.

The antibody the researchers used to bring about the conformational change binds to the T cell receptor and makes the T cells into tumor killers: "In many experiemtns, the pancreas tumor cells were all dead after five hours. With the method researchers previously used to activate γδ T cells, only 40 percent of the tumor cells were dead," says Wolfgang Schamel. "Our findings demonstrate that while conformational changes in the T cell receptor are not absolutely necessary for the functions of the immune defense, they do enhance the anti-tumor effect of the T cells."

Original publication:

Dopfer E.P., et al. (2014) The CD3 conformational change is not required for γδ T-cell receptor activation, but enhances tumor killing. Cell Reports

Caption:

If an antigen, a substance recognized as being alien to the body, binds the T cell receptor of γδ T cells, unlike in other T cell types, no reorganization of the protein occurs (blue). By use of an antibody Schamel and his team managed to induce this reorganization (red). This reaction enhances the tumor killing capacity of t cells.

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