

Self-regulation of the immune system suppresses defense against cancer

Regulatory T cells (Tregs), which are part of the body's immune system, downregulate the activity of other immune cells, thus preventing the development of autoimmune diseases or allergies. Scientists at the German Cancer Research Center (DKFZ) have now found the activation steps that are blocked by Tregs in immune cells. Since Tregs can also suppress the body's immune defense against cancer, the findings obtained by the DKFZ researchers are important for developing more efficient cancer treatments.

It is vital that the body's own immune system does not overreact. If its key players, the helper T cells, get out of control, this can lead to autoimmune diseases or allergies. An immune system overreaction against infectious agents may even directly damage organs and tissues.

Immune cells called regulatory T cells ("Tregs") ensure that immune responses take place in a coordinated manner: They downregulate the dividing activity of helper T cells and reduce their production of immune mediators. "This happens through direct contact between regulatory cell and helper cell," says Prof. Peter Krammer of DKFZ. "But we didn't know yet what this contact actually causes in helper cells." The researchers' hypothesis was that the contact with the Tregs affects certain steps in the complex signaling cascade that leads to the activation of the helper T cells.

If the T cell receptor, a sensor molecule on the surface of helper cells, senses foreign or damaged protein molecules, this will trigger a cascade of biochemical activation reactions. At the end of this signaling cascade, genes that are required for an immune attack will be read in the nucleus of helper cells.

Jointly with colleagues from several German research institutes, Peter Krammer, Angelika Schmidt and co-workers have now compared the signaling cascades in helper cells with and without contact to Tregs. The immunologists found out that a short contact of the two types of cells in the culture dish is sufficient to suppress the helper cells. Following Treg contact, the typical release of calcium ions into the plasma of helper cells does not occur. As a result, two important transcription factors, NFkappaB and NFAT, do no longer function. They normally activate genes for immune mediators, thus alerting the immune system.

"The mode of action of Tregs is of great importance for cancer medicine. Many of our colleagues have shown in various types of cancer that Tregs can downregulate the immune response against tumors so that transformed cells escape the immune defense. This can contribute to the development and spread of cancer. We are therefore searching for ways to reactivate such suppressed helper cells," said Krammer, explaining the goals of his work. For developing immune therapies against cancer it is also crucial to understand how Tregs work. The researchers are trying to prevent that immune cells which have been painstakingly activated against cancer in the culture dish are immediately suppressed again by Tregs.

Angelika Schmidt, Nina Oberle, Eva-Maria Weiß, Diana Vobis, Stefan Frischbutter, Ria Baumgrass, Christine S. Falk, Mathias Haag, Britta Brügger, Hongying Lin, Georg W. Mayr, Peter Reichardt, Matthias Gunzer, Elisabeth Suri-Payer and Peter H. Krammer: Human Regulatory T Cells Rapidly Suppress T Cell Receptor-Induced Ca²⁺, NF-κB and NFAT Signaling in Conventional T Cells. *Science Signalling* 2011, DOI: 10.1126/scisignal.2002179

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 2,500 employees is the largest biomedical research institute in Germany. At DKFZ, more than 1,000 scientists investigate how cancer develops, identify cancer risk factors and endeavor to find new strategies to prevent people from getting cancer. They develop novel approaches to make tumor diagnosis more precise and treatment of cancer patients more successful. Jointly with Heidelberg University Hospital, DKFZ has established the National Center for Tumor Diseases (NCT) Heidelberg where promising approaches from cancer research are translated into the clinic. The staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. The center is a member of the Helmholtz Association of National Research Centers. Ninety percent of its funding comes from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

Dr. Stefanie Seltmann
Head of Press and Public Relations
German Cancer Research Center
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2854
F: +49 6221 42 2968
presse@dkfz.de