Transgenic mice with with highly effective components of the human immune system

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How can the immune system be made more potent against cancer? To solve this crucial question, Dr. Liang-Ping Li and Professor Thomas Blankenstein of the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch and Charité - Universitätsmedizin Berlin in Germany have dedicated ten years of research to develop a new method. The researchers modified T cell receptors (TCRs), the antenna-like structures of T cells, so that they would no longer ignore cancer cells, but instead specifically track and recognize them. This modification is the precondition for the immune system to destroy cancer cells. The researchers developed a mouse with a whole repertoire of these human T cell receptors with the aim of utilizing these receptors in the future for targeted immunotherapy in patients.

The T cells of the immune system possess receptors on their surface with which they can recognize bacteria, viruses, and fungi and which enable the immune system to fight against foreign invaders and destroy them. At the same time, however, T cells must differentiate between "self" and "foreign" - between the body's own proteins and foreign proteins - so that the immune system tolerates the body's own tissue. If the immune system is no longer able to make this differentiation, it attacks "self" structures, leading to autoimmune diseases such as type 1 diabetes or multiple sclerosis.

In cancer diseases, however, the immune system appears to be restricted in its response. Cancer cells originate from the body's own tissue, which is why the immune system obviously has trouble recognizing them - and

that, although cancer cells often have antigens (from the Greek word antigennan meaning "produce against") which make them recognizable as tumor cells and pathologically altered cells.

Professor Thomas Blankenstein and his research team at the MDC and Charité want to break this tolerance towards cancer cells. In their research they utilized a process which in mammals automatically makes mature immune cells out of immature T cells. Immature T cells do not yet possess any T cell receptors and thus have to migrate from the bone marrow to the thymus. In this gland, which is part of the immune system, the T cell receptor genes, with which the T cell recognizes antigens, undergo random gene rearrangement.

Each of the millions of generated T cells expresses only one T cell receptor on the cell surface with which an antigen is recognized. In the thymus, however, all T cells which recognize "self" structures are deactivated. T cells which specifically target foreign antigens are spared from these tolerance mechanisms. The mouse, for example, does not develop any tolerance toward human cancer cell antigens.

"Probably no other transgenic mouse has that many human gene segments"

T cell receptors (TCR) consist of an alpha and a beta chain. Professor Blankenstein and his research team increased the DNA building blocks of humans for these chains with the aid of an artificial chromosome (YAC - yeast artificial chromosome) and then introduced them into embryonic stem cells of the mouse. Altogether there were approximately 2 million DNA building blocks, corresponding to 2 megabases or around 170 gene segments. "Probably no other transgenic mouse has that many human gene segments," said Professor Blankenstein.

Transgenic mouse with human T cell receptors

In ten years of developmental work the researchers in Berlin used embryonic stem cells loaded with human DNA to breed transgenic mice, which possess all possible human T cell receptors on their T cells. "These human T cell receptors in the mouse recognize human antigens of human cancer cells. For the mice human tumor antigens are foreign," Professor Blankenstein explained. "Such highly effective T cell receptors do not exist in humans. They are destroyed in humans in order to prevent them from attacking the body's own structures. Only T cells remain with less effective T cell receptors," he stressed.

The researchers aim to isolate these high-affinity human T cell receptors of the mouse, for which human cancer antigens are foreign, and to introduce them into the T cells of cancer patients. In this way the patients' ineffective T cells shall be boosted in their effectiveness to destroy the cancer cells. In contrast to a bone marrow transplantation, in which many T cells of the transplant are activated in the recipient, which can lead to life-threatening destruction of healthy cells, this therapy approach is very selective. With this method the researchers hope to avoid an overreaction of the immune system.

Whether the highly upgraded human T cells from the mouse preserve their great effectiveness in humans remains to be seen. At present the researchers are preparing a first clinical trial, in which they will test the effectiveness and tolerance of these T cell receptors in cancer patients.

More information: Liang-Ping Li, J. Christoph Lampert, Xiaojing Chen, Catarina Leitao, Jelena Popović, Werner Müller and Thomas Blankenstein, "Transgenic mice with a diverse human T-cell antigen receptor repertoire", Nature Medicine, doi: 10.1038/nm.2197