Healthcare industry BW

Arming the immune system against cancer

The theory that immune cells are able to attack tumours has long been a theory with only a minority of supporters. However, this theory is currently experiencing a renaissance. In the future, it might even be possible to specifically alter T-lymphocytes in order to improve their ability to identify and destroy certain tumour types. Prof. Dr. Hanspeter Pircher and his team at the Freiburg University Medical Centre are focusing on the development of methods for passive cellular immunisation: Can their methods provide the immune system with external weapons to destroy tumours and if so, which methods are the most effective ones?

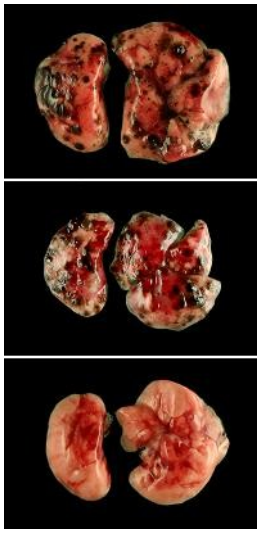
Recent experimental evidence appeared to support the theory: genetically modified mice, which lacked T-cells for example, developed more tumours than unmodified mice. This experimental finding led to the revival of the immune surveillance theory proposed in the 1960s, which stated that abnormal cells activated cells of the immune system, which then prevented the formation of spontaneous tumours. However, the tumour cells mutate and alter their surface structure. The body's own guards no longer recognise the tumour cells and the tumours can grow undisturbed. "We believe that this theory is correct," said Prof. Dr. Hanspeter Pircher from the Institute of Microbiology and Hygiene at the Freiburg University Medical Centre. "We are therefore trying to find out how the immunological tumour defence can be strengthened."

Active or passive immunisation?

Active immunisation is one of the possible ways to strengthen immunological tumour defence. It is a process that has long been used in vaccinations against influenza viruses and tetanus. Doctors apply antigens into the muscles of patients. Antigens are components of the infectious pathogens and are rather like an identity card that is recognised by the immune system. These antigens activate the immune system in the lymph nodes. This leads to the production of specific antibodies that attack the intruders. "The problem of active immunisation is that many vaccines only trigger the production of sufficient quantities of antibodies," said Pircher. "However, diseases such as AIDS, malaria, tuberculosis or cancer can only be effectively treated if T-lymphocytes are also activated. And this is difficult to achieve with standard immunisation methods.

Since active immunisation can only be achieved with sophisticated tricks, Pircher and his team have focused on passive cellular immunisation, which involves the direct administration of immune cells. In principle, there are two methods that can be used to combat the tumours. One method is to isolate T-lymphocytes directly from the tumour tissue of the cancer patient. These T-lymphocytes are already primed against the patient's particular tumour and have developed specific receptors that recognise the tumour antigens. The T-lymphocytes are expanded in cell culture before they are returned to the patient in a more concentrated form. However, currently available methods are unable to provide a high enough quantity of cells to ensure the sufficiently long-term survival of the cells following the adaptive transfer into the patient. Therefore, Pircher and his PhD student Katja Müller are investigating the conditions under which the cells can be particularly well expanded. They found that this depends on the presence of the T-cell growth factor interleukin 15 (IL-15).

Not fattened up so much

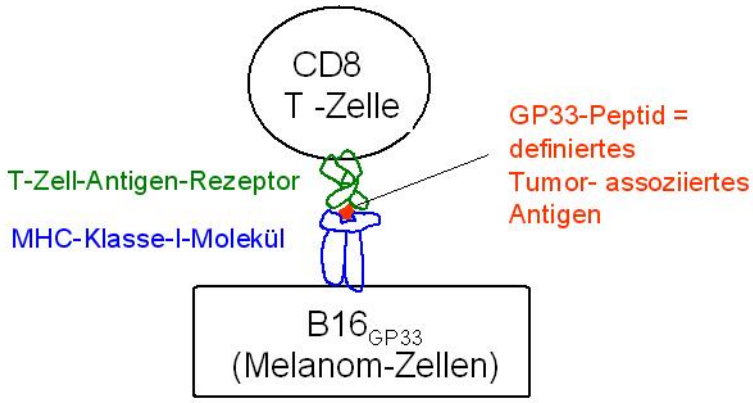


Mouse lungs with tumour colonies: without T-cell transfer (above), after the transfer of IL-2-activated T- cells (centre) and after the transfer of IL-15-activated T-cells.

In contrast to cells that are fed with a similar molecule, i.e. interleukin 2 (IL-2), the T-lymphocytes that are fed with IL-15 are relatively small and not very aggressive. But when the scientists injected the cells into living mice with a model tumour, the cells displayed a much greater efficiency: The mice developed a smaller number of lung metastases than the mice whose T-lymphocytes were cultivated with IL-2. "We assume that T-cells that are grown in media with IL-15 do not fatten up as much as the others," said Pircher. "We therefore assume that these cells depend less on food in the living organism than the T-cells fed with IL-2, and therefore do not die so easily."

The second possibility for passive immunisation is to prime T-lymphocytes that have not been in contact with a tumour from the outside. The basic idea behind this is that the naïve T-cells are equipped with a probe that enables them to recognise certain tumour cell types. If the cells succeed in recognising certain

tumour cells, they start to eliminate them. "Retroviral gene transfer has been shown to be a very suitable method for this purpose," explained Pircher. Pircher's cooperation partner, Prof. Dr. Wolfgang Uckert from Berlin, is able to introduce genes of special T-cell antigen receptors into the genome of retroviruses. These receptors are very specific. In Pircher's model system, the receptors react exclusively with the short protein piece Gp33, which is located on the surface of tumour cells (antigen). Pircher and his team are then able to transfer the retroviruses into the lymphocytes of the cancer mouse models. Retroviruses are known for their ability to incorporate their genome into the DNA of their host cells. In so doing, they also introduce the gene of the antigen receptor, and enable the T-cells to produce the antigen receptor themselves.



T-cell (top) loaded with antigen receptors. It recognises the tumour antigen on the surface of a tumour cell (bottom) according to the key-lock principle.

“However, this method is not yet sufficiently established,” said Pircher. “At present, the density of the transduced receptors on the surface of the T-cells is not yet high enough.” Therefore, the tumour model-specific T-cells are still unable to provide effective protection against the tumour. The problem is that the tumour cells only have a small number of antigens on their surface and the T-cells should be far more sensitive. But it has already been shown that they provide protection against viruses with a higher density of surface antigens. However, in order to confer effective protection against tumours, the scientists need to produce T-cells with a much higher density of antigen receptors. “In future, we would like to combine the two methods,” said Pircher. This means that the researchers will have to treat the T-cells with retroviruses and equip them with the respective receptors, cultivate them in culture dishes under optimal conditions and with sufficient quantities of IL-15 and finally select the receptors with the highest receptor density.

Starving the tumour

If the researchers succeed in combining the two methods, they will have come a step closer on their path to finding an effective anti-cancer immunotherapy. Additional experiments carried out by Pircher and his team have shown that T-lymphocytes are able to destroy tumours from the inside. But how do the T-lymphocytes do this? It might be assumed that the lymphocytes destroy the membrane of tumour cells upon contact, thereby destroying them. Another possibility might be that they attract other cells of the immune system, for example macrophages or natural killer cells. However, Pircher and his colleagues believe that the mechanism is more an indirect than a direct one. “We assume that the T-cells release substances such as interferon gamma upon contact with a tumour,” said Pircher. “And this then prevents the blood vessels in the tumour from growing.” Without sufficient blood supply, the tumour starves and eventually dies.

It is assumed that these mechanisms also play a role in humans. Pircher and his team hope that their findings will be used by clinical researchers. “Maybe, we will at some time in the future have a fridge where we store suitable retroviruses with the respective antigen receptor genes for any tumour,” said Pircher. These are still very much dreams of the future. In addition, Pircher believes that immunotherapy alone will have no effect. In terms of solid tumours, the effective destruction of tumours will need to involve a combination of surgical methods and chemo- or radiotherapy.

Further information
Prof. Dr. Hanspeter Pircher
Institute of Medical Microbiology and Hygiene
Department of Immunology
University of Freiburg
Hermann-Herder-Str. 11
D-79104 Freiburg
Tel.: +49 (0)761/203-6521
Fax: +49 (0)761/203-6577
E-mail: hanspeter.pircher(at)uniklinik-freiburg.de