Live coverage of the immune system at work

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To better understand what happens during immune reactions in the body, researchers at Tübingen University have developed a new way of labeling T-cells, allowing them to track the T-cell movement in mice using non-invasive positron emission technology (PET). The researchers, led by Professor Bernd Pichler at the Werner Siemens Imaging Center, worked with dermatologists, pathologists and immunologists at the University hospitals and at the German Consortium for Translational Cancer Research. They describe the new technique in the latest issue of *PNAS*.

The immune system's T-cells are a key starting point for researchers developing immunotherapies against cancer and autoimmune diseases. T-cells are constantly on the move throughout the body, checking for invading pathogens and diseased cells. If any of these structures which fit the T-cells' specific receptors like a key fits the right lock – then the T-cell will proliferate and set off a series of signals, starting the process of eradicating the diseased cell. Each T-cell recognizes just one specific pattern on the cell's surface and there are thousands of different T-cells. If the T-cells miss their target or if they mistakenly order the destruction of a healthy cell, the result will be disease in the form of infection, cancer, allergies or auto-immune conditions.

Previous methods used to follow the movement of T-cells by PET impaired or even damaged the cells. In this latest study, the researchers placed an antibody with a weak radioactive component onto the receptors on the T-cells' outer membrane. This radiation could be seen and measured by the PET device. T-cells constantly recycle the receptors on their outer membrane, transporting them inside the cell – in this case, along with the radioactive marker. "The blocked T-cell receptor is no longer available to recognize the specific antigen," says the study's lead author, Dr. Christoph Griessinger. "But the specific receptors are quickly resupplied and the immune reation is barely impaired." The researchers have about 48 hours to take their measurements – after that, the radioactive material has largely decayed and the radiation is too weak.

"The marker remains stable in the T-cell for that time," project leader Dr. Manfred Kneilling explains. The T-cells' functions are barely hindered despite the marker – and PET technology provides high-contrast images. The researchers were able to watch live coverage of how the T-cells targeted and specifically migrated into infected tissue. Supported by comparative control testing, in which the researchers induced inflammation using very similar antigens not matching the specific T-cell, they were able to prove that T-cells only migrate into tissue inflamed by their specific antigen.

"This technique could be applied to other cell types of the immune system – anywhere the receptors on the membrane are renewed often," says Griessinger. There are already plans to apply the technique in humans. Imaging techniques are becoming ever more important in the fields of cellular immunotherapy and stem-cell transplantation, the researchers say. For instance, imaging could be used in new cancer treatments in which the patient's own immune system is employed to target tumor cells. "We would be able to mark the treated immune cells as we did the T-cells and to track whether they migrate to the tumors as planned," says Kneilling.

More information: "64Cu antibody-targeting of the T-cell receptor and subsequent internalization enables in vivo tracking of lymphocytes by PET." *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1418391112

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