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Antibody armed with a viral protein enhances cancer therapy

Scientists from the German Cancer Research Center (DKFZ) and the Helmholtz Zentrum München are exploring new ways to fight lymphoma. They have developed a new method that simulates a viral infection of cancer cells. The immune cells activated as a result are able to kill the cancer cells efficiently.

The medical term “non-Hodgkin lymphoma” refers to a group of over 20 different cancers of the lymphatic system. These cancers usually start in B lymphocytes that have undergone malignant transformation. “The cure rate for lymphoma is about 70 percent today. In relapsing lymphomas, however, we are still lacking better therapies to help patients,” says Professor Henri-Jacques Delecluse of the DKFZ. “We are therefore trying to find new methods to enhance the body's own immune system in fighting lymphoma cells.”

Delecluse's group, working together with Josef Mautner and Regina Feederle from the Helmholtz Zentrum München, have been searching for ways to label lymphoma cells in a special way that makes them more visible to the immune system. To this end, the researchers made use of antibodies that distinctively exhibit a piece of viral protein.

These antibodies contained binding sites that target specific molecules on the surface of the lymphoma cells. The researchers had used genetic engineering methods to fuse protein pieces of Epstein-Barr virus (EBV) to the “rear” end of the antibody protein. Exposure to EBV is very common, so many people already have memory T cells that can mount a rapid and powerful immune response upon a new encounter with this pathogen.

The antibodies attach via their binding sites to the cancerous B cells and are subsequently engulfed into the cell interior. There, the antibody protein is degraded and the individual fragments are presented by special molecules on the surface of the cancer cells. As a result, the viral protein is also exhibited on the cell surface, thus making it look like an EBV infection to the immune system.

A viral infection is an alarm sign that T cells cannot ignore. In a Petri dish, the researchers found that T cells effectively killed the “infected” lymphoma cells. When the investigators obtained blood cells from individuals who had been infected with Epstein-Barr virus in the past, they succeeded in using the antigen-armed antibodies to activate memory T cells. “This is a clear indication that our antigen-armed antibodies can also induce an immune response against lymphoma cells in a living organism,” explains Delecluse.

Depending on one's genetic makeup, the EBV protein fragments presented on the cell surface can vary between individual people. In order to activate the immune system in as many people as possible, Delecluse and colleagues also inserted larger pieces of EBV proteins into their antibodies. Depending on their genetic makeup, the cells could then cut out various smaller protein segments and present them on their surface.

“A problem with antibody-based cancer therapies is that the tumor cells make the surface molecule targeted by the antibody disappear from their surface,” says Delecluse. Explaining the benefits of his treatment approach, he continues: “To prevent this situation, we used a mixture of antibodies that target four different B cell surface molecules.”

Antigen-armed antibodies were initially developed as a vaccine to immunize people against pathogens. "We have now shown for the first time that they can also be used as a tool in cancer therapy, not only against B cell lymphoma but potentially also against other types of cancer."

Xiaojun Yu, Marta Ilecka, Emmalene J. Bartlett, Viktor Schneidt, Rauf Bhat, Josef Mautner, Regina Feederle and Henri-Jacques Delecluse: Antigen-armed antibodies targeting B lymphoma cells effectively activate antigen-specific CD4+ T cells. Blood 2015, DOI: 10.1182/blood-2014-07-591412

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 3,000 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. The staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. 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. In the German Consortium for Translational Cancer Research (DKTK), one of six German Centers for Health Research, DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients. DKFZ is a member of the Helmholtz Association of National Research Centers, with ninety percent of its funding coming from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

Contact:

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

Dr. Sibylle Kohlstädt
Press and Public Relations
German Cancer Research Center
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2843
F: +49 6221 42 2968
Email: presse@dkfz.de