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No. 07 February 5, 2015 (Koh)

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

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