New vaccine boosts natural killer T cells in patients with cancer

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A new vaccine designed at The Rockefeller University boosted a type of fast-responding immune system cell called the natural killer T (NKT) cell in patients with advanced cancer. The study surprised researchers by revealing the ability of these NKT cells to spur other, slower-responding immune cells to go to work.

The findings are encouraging researchers at Rockefeller to pursue additional clinical research using the new NKT approach to improve T cell based vaccines against cancer and viral infections.

Results of this study are published in the May 2 issue of the Journal of Experimental Medicine.

The study began in July 2003 and treated 5 patients with advanced cancer who had no detectable NKT cells in their blood at the start of the study. The experimental vaccine led to considerable expansion of NKT cells in all patients that lasted for at least 3 months.

"This study clearly demonstrates the feasibility to specifically boost this important immune cell in humans and therefore opens the door for targeting the innate arm of the immune system against pathogens and cancer," says Madhav Dhodapkar, M.D., who led the study and heads the laboratory of Tumor Immunology and Immunotherapy at the university.

The duration of the expansion was also unexpected, says co-author Ralph Steinman, M.D., head of the Laboratory of Cellular Physiology and

Immunology at Rockefeller, because most NKT cell responses are short-lived.

The power of NKT cells lies in their capacity to prompt many infection- and disease- fighting immune cells downstream of their initial, speedy response. This effect may be what's happening with the application of the new vaccine, according to the researchers.

The vaccine led to enhancement in what's known as adaptive immunity, the immune response that does not take place immediately, but is more fine-tuned to specific foreign invaders like microbes or mutated cells.

NKT cells are part of what's known scientifically as the innate immune response, or that part of the immune response that should, under normal circumstances, respond quickly. Most prior cancer vaccines have focused on the adaptive immune system. What's more, prior attempts to mobilize NKT cells in humans have met with limited success.

"Early events of the immune system may determine what happens down the line," says Dhodapkar. "In cancer, we've learned that both arms of the immune system are defective." The absence of a coordinated immune response may allow cancer cells to grow and spread.

Using mature dendritic cells might be one of the keys to attaining consistent results, says co- Steinman, a senior Rockefeller University scientist who discovered the dendritic cell in 1973. "The interaction of mature dendritic cells with NKT cells results in the production of many immune-enhancing cytokines," he says. Cytokines are molecular messengers produced by white blood cells, including dendritic cells, and they are an important part of the immune system's complex communications system. When scientists elsewhere carried out an experiment similar to the current study, but used immature dendritic cells, results were limited and not consistent.

Naturally occurring mature dendritic cells are known to do two things: one is to process and present antigen, or material considered foreign to the body. This presentation allows other immune system cells to recognize foreign material, which includes tumor cells. The other activity of the mature dendritic cell is to deliver "accessory" signals to immune system cells so that they expand or differentiate, or develop into, helpers or killers focused on removing an antigen. Cytokines are examples of these accessory signals. Mature dendritic cells used in the experimental vaccine may possess the correct chemical vocabulary with which to speak.

The Rockefeller researchers now are planning another clinical study in a larger population of cancer patients using their new strategy.

In any clinical study, the first question is whether you can safely and reliably achieve a therapeutic goal. The current study is an important first step. The next step will be to build on this approach to improve clinical efficacy, both by improving the function of expanded NKT cells and the downstream recruitment of T and NK cells. "Fortunately, we already have several new insights from the bench along these lines that are ready to be translated to the bedside," says Dhodapkar. "The next challenge is to test these approaches in our patients."

"The principle of this vaccine is valid for both cancer and infectious disease. These findings therefore support testing this strategy in chronic viral infections such as HIV or hepatitis C," says Dhodapkar.

The process for creating the vaccine used in this investigation is known as ex vivo amplification. Scientists at Rockefeller University and elsewhere have devised methods to expand patients' own dendritic cells outside of their bodies, expose the cells to antigen or load them with powerful drugs, and send them back inside the body to deliver emphatic messages or finely tailored treatments. Because the dendritic cell is at the

heart of the immune system's operations, it is capable of more precise control of immune mechanisms and better delivery than traditional treatments that send antigen or drugs randomly into the bloodstream. KRN-7000 (manufactured by Kirin Breweries, Japan), the drug used in this study, is known to be safe, but was not effective at expanding NKT cells in prior trials when used alone. Specialized delivery via dendritic cells arguably makes the difference in the drug's efficiency.

While the ex vivo dendritic cell approach is exciting, it also is slow-going, says Steinman. "If we were better able to manipulate dendritic cells, we could create many different strategies for controlling different aspects of immune system function."

Additional Rockefeller University co-authors are David H. Chang, Keren Osman, Anjli Kukreja, Joseph Krasovsky, Aisha Hutchinson, Matthew Geller, Nancy Liu, Rebecca Annable and Kelly Kirchoff.

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