New Strategy Produces Promising Advance in Cancer Vaccines

February 15 2010

(PhysOrg.com) -- Researchers at National Jewish Health and the University of Colorado Denver used a new strategy to develop cancer vaccines that were remarkably effective in mice.

In the February 16 issue of the Proceedings of the National Academy of Sciences *(PNAS)*, Kimberly Jordan, PhD, Jill Slansky, PhD, and John Kappler, PhD, report that 100 percent of the mice vaccinated with a peptide they developed remained alive and tumor-free for at least 60 days after inoculation with colon cancer cells. The research suggests a method for developing vaccines against a wide variety of cancers.

"We developed a peptide vaccine that binds strongly to naturally occurring T cells and stimulates them to vigorously attack cancer cells in mice," said Dr. Slansky, Associate Professor in the Integrated Immunology Department at National Jewish Health and the University of Colorado School of Medicine. "We can't guarantee that the vaccines we developed will make it to human trials, but our work does show that very effective cancer vaccines can be made, and outlines a new strategy for their development."

T cells are one of the prime sentinels of the immune system, which sound the alarm and help orchestrate the immune response. Ever since scientists found T cells inside tumors, they realized that the body does have a natural, albeit mild, immunity to cancer. The T cells inside tumors recognize antigens on the surfaces of tumor cells, but don't bind them strongly enough to sound an alarm or initiate a robust immune response.

Scientists have tried several strategies to stimulate those T cells, from general immune stimulants to synthetic variations on the naturally occurring antigens. Although some of the vaccines showed moderate results in animal models, none has proven effective in humans.

Dr. Slansky hypothesized that previous vaccine candidates were unsuccessful because they did not bind strongly enough to the T cells found inside tumors. As a result, the vaccines failed to stimulate the T cells into mounting an effective immune response. So, she, structural biologist Dr. Kappler, and Dr. Kimberly Jordan, the postdoctoral fellow whose work bridges the two labs, designed peptide vaccines that resemble naturally occurring antigens but bind more strongly to the T cells found inside tumors.

They evaluated five candidate peptide vaccines. They vaccinated mice twice with the candidate vaccines, then injected colon tumor cells into the mice a week later. The results were quite variable. Two of the vaccines protected few or no mice, three other vaccines kept 60%, 90% and 100% alive and tumor-free for 60 days.

The researchers tried to learn what distinguished the effective peptide vaccines from ineffective ones. They found that the ineffective vaccines strongly stimulated T cells that recognized the peptide vaccine but not any T cells that recognized antigen on the cancer cells.

The successful vaccines stimulated T cells that recognized both the peptide vaccine and the naturally occurring antigen. The successful antigens stimulated the growth of many more T cells than the ineffective ones. Those T cells were also highly activated and ready to attack, as evidenced by their production of cytokine signaling molecules. Remarkably, the most successful vaccine varied by only one amino acid from the naturally occurring antigen, which provoked almost no immune response.

"Our theory about the importance of the T cell-peptide bond was correct, but we learned that the peptides must also stimulate T cells that cross react with the existing antigens and produce a large population of activated T cells," said Dr. Kappler. "We believe this provides a very promising strategy for developing cancer vaccines. We are now working to learn why a single-amino-acid substitution makes such a huge difference in effectiveness."

The research was supported by grants from the American Cancer Society, the National Cancer Institute and Cancer Research Institute.

Provided by National Jewish Health