One cell type may quash tumor vaccines

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Most cancer vaccines have not lived up to their promise in clinical trials. The reason, many researchers suspect, is that the immune cells that would help the body destroy the tumor – even those reactions boosted by cancer vaccines – are actively suppressed. Now, researchers at Thomas Jefferson University have found that a single cell type is actively suppressed in several experimental cancer vaccines, paving the way toward methods to break suppression and improve the effectiveness of cancer vaccines. The work was published this week online in the *European Journal of Immunology*.

"The conventional wisdom is that the body knocks out all of the cells that can mount an immune response to the cancer," says first author Adam Snook, PhD, a Research Instructor at Thomas Jefferson University. "In fact, our work shows that it's only one cell type that is affected. But that cell, the T-helper cell, acts as the lynchpin."

Cancer vaccines are designed to boost the body's natural defenses against cancer. They work by training the immune system to recognize and attack specific tumor peptides, which are a kind of identification tag for tumors. These peptide "tags" help the immune system find and attack cancer cells. There are three types of cells that can "see" and react to these tags: T-helper cells, cytotoxic T cells, and B cells, and researchers thought that all three were trained, or tolerized, to ignore the tags on cancer cells.

Dr. Snook and colleagues tested which cell was involved by inoculating mice with a cancer vaccine they developed for colorectal cancer using a tumor peptide called guanylyl cyclase C (GUCY2C). Normally, GUCY2C-vaccinated mice would not produce much of an immune response, from either T cell type or B cells. However, when the researchers boosted the GUCY2C vaccine by linking it to another peptide called S1 that efficiently activates T-helper cells, they were able to see a vigorous activation of cytotoxic T cells and B cells directed at GUCY2C.

In fact, the GUCY2C vaccine-S1 combo improved the survival time of mice with cancer by months compared to only days with GUCY2C vaccine alone. In fact, many mice were cured of their disease.

When Dr. Snook tested two other cancer peptides, one for breast cancer (Her2) and one for melanoma (Trp2), he saw similar results, suggesting that selective inactivation of T helper cells occurs for peptides found in many cancer types. "The results make a lot of sense," says Dr. Snook. "T-helper cells, as their name suggests, provide help to both cytotoxic T cells and to B cells. The entire peptide-specific immune response can be taken out by tolerizing this one cell type."

In addition, T-helper cells are also essential for creating immunological memory. Boosting T-helper cell activation also protected mice from challenge with cancer months after the initial vaccination, increasing their survival and decreasing tumor number.

The next step is to test whether a T helper peptide-linked GUCY2C vaccine could help fight colorectal cancer in humans. Dr. Snook and colleagues are currently enrolling patients in a clinical trial aimed at reducing the rate of cancer recurrence in patients who had their primary tumors removed.

More information: AE Snook, et al., "Self-tolerance eliminates CD4+ T, but not CD8+ T or B, cells corrupting cancer immunotherapy," *European Journal of Immunology*, DOI: 10.1002/eji.201444539, 2014.

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