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Unmasking and killing resistant tumors

Scientists at RIKEN improve an experimental therapy that harnesses the immune system to circumvent tumor resistance

In the battle against cancer, much attention has been directed at ways to help the body's own immune system recognize, reject and kill tumors. Unfortunately, progress has been impeded by the inherent complexity of the immune system.

Now, scientists from RIKEN's Research Center for Allergy and Immunology, led by Shin-ichiro Fujii, in collaboration with the Laboratory of Cellular Physiology and Immunology at Rockefeller University in New York, describe a strategy in *the Journal of Experimental Medicine*, that could help to significantly advance cancer vaccines, which are the focus of increasing interest in the field of cancer immunotherapy.

Cancer immunotherapy takes advantage of one of the immune system's natural roles: detecting and killing precancerous cells. Of the many cell types comprising the immune system, the highly specialized dendritic cells (DCs) have recently taken center stage, especially in the emerging arena of cancer vaccines. The RIKEN team collaborated on this research with eminent Rockefeller University researcher Ralph Steinman, who discovered DCs. These cells are the key orchestrators of an activated immune response, which involves 'killer' T-cells (TKs) and other players working in concert to marshal appropriate defenses against threats within the body.

Early in the immune response, the DCs engulf and break up foreign organisms or unwanted self-cells before presenting the processed portions of the target, or antigens, to the TKs, thereby priming these killer cells to identify and attack the targets. During the intimate and elaborate 'embrace' underpinning this antigen presenting process, the cells exchange critical information using specific proteins on their surfaces as part of a highly sensitive system of checks and balances.

Many malignant tumors escape immune attack by capitalizing on this rigorous regulation to instill, in key effectors, a form of 'tolerance.' Such tumors have evolved elaborate mechanisms of subterfuge that routinely flummox what is otherwise a highly sophisticated and effective system of immunity.

Fujii's group developed a cancer vaccine that, in effect, turns off the braking signals deployed by such resistant tumors. The main challenge with cancer vaccines has been finding effective cancer-associated antigens - often a frustrating hit-and-miss process - that can be appropriately packaged to induce sufficiently strong and persistent anti-tumor immune responses. To address this, the scientists utilized whole tumor cells coated with alpha-galactosylceramide (AGC) - a chemical glycolipid that specifically activates very specialized killer cells called NKTs - to create a potent new type of vaccine. The researchers demonstrated that mice administered this specialized vaccine were protected from four different types of lethal tumors.

The scientists injected single loads of one type of AGC-modified tumor cells, intravenously, into mice that were then inoculated, several weeks later, under the skin, with active tumor cells. Unvaccinated mice succumbed rapidly to these aggressive tumors but vaccinated mice not only survived but their resistance to these tumors also persisted for 6-12 months, an eternity for such short-lived animals. The same results were duplicated using three other tumor cell types.

Moreover, in contrast with other methods, this effective strategy utilized a low load of tumor cells, a critical safety consideration in cancer vaccines. This vaccine's potency hinges on NKTs and the capture and presentation of AGC by DCs: NKTs rejected the AGC-loaded tumor cells, setting off a complex cascade of stimulatory signals anchored and mobilized by several subsets of DCs, culminating in long-term T-cell based immunity.

Because AGC seems to be safely tolerated in patients, and since AGC-coated tumor cells first killed by irradiation were also effective in immunizing mice, Fujii and his colleagues believe that clinical trials using this approach can be safely attempted to identify the most effective tumor cell types that can override tumor tolerance. Such cancer vaccines may soon be added to our arsenal against cancer.

Original work:

Shimizu, K., Kurosawa, Y., Taniguchi, M., Steinman, R. and Fujii, S. Cross-presentation of glycolipid from tumor cells loaded with galactosylceramide leads to potent and long-lived T cell-mediated immunity via dendritic cells. *The Journal of Experimental Medicine*, published online on Oct. 19, 2007.

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