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Gene that suppresses cell's immune activation identified

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(PhysOrg.com) -- A new study of prostate tumors has shown that a gene, FOXO3, suppresses activation of cells related to immunity and thus leads to a reduced immune response against a growing cancer. One of the main problems in treating cancer by vaccine or immunotherapy is that tumors often evade the body's immune response — and one of their tricks is to create an environment where immunity is inhibited or suppressed. By identifying a gene that makes immune cells suppressive, the researchers may have found a new target for enhancing immune responses to cancer tumor cells. The study, by scientists from the National Cancer Institute (NCI), part of the National Institutes of Health, appeared online March 23, 2011, in the *Journal of Clinical Investigation*, and in print April 1, 2011.

The cells isolated and examined in this study were dendritic cells. These cells normally initiate an immune response to disease by presenting a foreign protein (or antigen) in a way that it is recognized by an invader-killing T cell. In tumor-associated dendritic cells, however, this stimulating immune response is often suppressed.

To overcome the problem associated with tumor-associated dendritic cells, Arthur A. Hurwitz, Ph.D., head of the Tumor Immunity and Tolerance Section, NCI, and postdoctoral fellow Stephanie K. Watkins, Ph.D., conducted a series of experiments aimed at enhancing immunity to tumors. As a result, they discovered that prostate tumors from mice contained a population of dendritic cells that express FOXO3 at high levels. These dendritic cells no longer activated T cells. Instead, they

muted the immune response, which caused the T cells to become tolerant of tumor cell antigens, to lose their ability to target and kill tumor cells, and even to suppress the activity of other T cells. Under certain conditions, elimination of the suppressive dendritic cells led to reduced tumor size. The findings made in mice then led the research team to examine human prostate tumors in the lab where they found similar dendritic cells with high FOX03 levels.

In past studies, Hurwitz and his colleagues worked to identify how tumors evade recognition by the immune system. Their results showed that, in the same mouse model of prostate cancer, T cells become tolerant upon entering a tumor and acquire the ability to suppress other T cells.

In this study, the scientists demonstrated not only that dendritic cells isolated from tumors were poor at initiating immune responses, but also that these cells were responsible for inducing T cell tolerance and converting them to suppressor T cells. Using microarray technology, a technique that allows scientists to examine the expression of thousands of genes simultaneously, they compared the genes expressed by the tumor-associated dendritic cells to those expressed by dendritic cells in normal tissue. Among the genes that were overexpressed in the tumor-associated dendritic cells, FOXO3 was an appealing candidate for an immune modulator because it was known to be a regulator associated with dendritic cell function. When FOXO3 gene expression was silenced in the tumor-associated dendritic cells, the scientists found that these cells no longer had an immune suppressive function but rather initiated appropriate immune responses.

“Our research suggests that it may be possible to boost immune responses to tumors and prevent immune suppression if we target FOXO3, either directly or with prostate and other cancer vaccines. This might be achieved by using small molecule drugs or peptides that target

FOXO3 in dendritic cells or by silencing FOXO3 expression in dendritic cell vaccines that already exist, making them more potent," said Hurwitz. "We believe this finding could also be applied to treating autoimmune diseases, where therapies aimed at inducing immune suppression may benefit from enforcing expression of FOXO3."

This work has led to the submission of a patent application by the NIH on behalf of Hurwitz and Watkins to target FOXO3 as a way to boost immune responses in cancer and to silence excessive immune responses in autoimmune diseases. While waiting for patent approval, the scientists will study how tumors, or the tumor microenvironment, induce FOXO3 expression as well as how FOXO3 induces this suppressive activity.

More information: Watkins, SK, et al., FOXO3 programs tumor-associated DCs to become tolerogenic in human and murine prostate cancer, *Journal of Clinical Investigation*, April 2011, DOI: 10.1172/JCI44325

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