

Prostate Tumors Can Change the Function of Immune Cells in Mice

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(PhysOrg.com) -- Researchers have discovered that prostate tumors in mice can cause immune cells known as CD8+ T cells to change their function from cells that have antitumor activity to cells that suppress immune responses. This finding, by researchers at the National Cancer Institute (NCI), part of the National Institutes of Health, has important implications for the design of immune-based therapies for cancer.

The new study, available online, appears in the Oct. 15, 2009, issue of the [Journal of Immunology](#).

"The conversion of CD8+ T cells into suppressor cells may be one of the mechanisms by which tumors restrict the immune system's ability to control [tumor growth](#)," said Arthur A. Hurwitz, Ph.D., head of the Tumor Immunity and Tolerance Group at NCI's Center for [Cancer Research](#). "Studying this process in mice may help explain why some cancer patients have an initial response from their immune-based therapy, but this response fails with time."

In mice and humans, when the immune system encounters a pathogen or other foreign invader, it responds by mounting an immune response. Part of this response involves the recruitment and activation of CD8+ T cells, which are also called cytotoxic T cells or killer T cells, to help destroy the invader. CD8+ T cells also play a role in immune responses against tumor cells. Other T cells, known as CD4+ T regulatory cells, work to suppress CD8+ T cell activity. Immune suppression by these regulatory T cells helps prevent the body from attacking its own cells. A high level

of CD4+ T regulatory cells is also associated with poor prognosis of some cancers. Moreover, research in mice has shown that blocking the immune suppressive activity of these [regulatory T cells](#) enhances the body's immunity against tumors, causing tumor growth to slow and improving the antitumor immune responses elicited by cancer vaccines.

Recent evidence in mice has suggested that CD8+ T cells can develop suppressive activities similar to those of CD4+ T regulatory cells. In addition, CD8+ suppressor cells have been found in cancer patients. The presence of these suppressor cells could explain earlier findings by Hurwitz's team that prostate tumor-specific CD8+ T cells injected into prostate tumor-bearing mice migrate to the tumors but then become unresponsive, or tolerized, to the tumor cells. It remained unclear, however, whether the suppressive CD8+ T cells have suppressor activity before they reach the tumor or whether they are converted into suppressor cells by the tumor.

In the new research, Hurwitz's team found that CD8+ T cells acquire immune suppressive functions after they enter the mouse tumor microenvironment, which encompasses nearby noncancerous cells and [immune cells](#) in addition to tumor cells. The researchers found that tumor-specific CD8+ T cells isolated from the tumors were able to suppress the proliferative capacity of nonspecific T cells, whereas tumor-specific CD8+ T cells isolated from lymph nodes of the mice were unable to do so.

This anti-proliferative activity appeared to be caused, in part, by substances secreted by the CD8+ T cells after they had been converted to suppressor cells. One of these substances, TGF-beta, is a protein that controls cell proliferation and differentiation and plays a role in cancer and other diseases. TGF-beta is thought to be involved in the immune-suppressive activity of CD4+ T-regulatory cells.

Next, the team investigated whether the conversion of tumor-specific CD8+ T cells to suppressor cells could be prevented. To do this, they administered tumor-specific CD4+ and CD8+ T cells to prostate tumor-bearing mice. Some CD4+ T cells act as helper cells and enhance the activity of other immune cells, including CD8+ T cells. The researchers found that, under these conditions, CD8+ T cells isolated from the [prostate tumors](#) no longer suppressed the proliferation of other T cells. Moreover, these cells produced less TGF-beta than cells that were not exposed to CD4+ T cells.

The researchers propose that activated CD4+ T cells that enter tumors may secrete factors that support the CD8+ T cell antitumor functions, or may help other immune cells located in the tumor block the processes by which CD8+ T cells acquire their suppressive activity.

Future work by this team will focus on defining the mechanisms by which tumor-specific CD8+ T cells gain their suppressive functions upon entering the mouse tumor microenvironment. "It is important to understand how these cells become suppressive and how they mediate suppression to find approaches to block these processes," said Hurwitz. "This will enhance our ability to generate more effective antitumor T cell responses in mice, which then might be translated to human."

More information: Shafer-Weaver, KA, Anderson, MJ, Stagliano K, Malyguine, A, Greenberg, NM, and Hurwitz AA. Cutting Edge: Tumor-Specific CD8+ [T Cells](#) Infiltrating Prostatic Tumors Are Induced to Become Suppressor Cells. *J Immunol.* Oct. 15, 2009. Vol. 183, No. 8.

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