Mechanism offers promising new approach for harnessing the immune system to fight cancer

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St. Jude Children's Research Hospital scientists have discovered a way to target the immune system to shrink or eliminate tumors in mice without causing autoimmune problems. Researchers also found evidence that the same mechanism may operate in humans. The study was published today in the advance online edition of *Nature*.

The findings provide a new target for ongoing efforts to develop immunotherapies to harness the immune system to fight cancer and other diseases.

The work focused on white blood cells called regulatory T cells. These specialized cells serve as the immune system's police force, working to control inflammation and guard against autoimmune and inflammatory disease. Regulatory T cells can, however, interfere with the immune system's ability to fight cancer.

In this study, investigators identified a mechanism that boosts the ability of regulatory T cells to cause problems by blocking an effective anti-tumor immune response. The same process, however, plays no role in maintaining immune balance or preventing the misguided immune attack on healthy tissue that leads to autoimmune problems, researchers reported. Blocking this mechanism led to the elimination or dramatic reduction of melanoma by the immune system in mice, without causing the autoimmune and inflammatory problems often associated with current cancer-treatment efforts that target immune regulators, scientists said.

"Regulatory T cells are a major barrier to effective anti-tumor immunity," said the study's corresponding author, Dario Vignali, Ph.D., vice chair of the St. Jude Department of Immunology. "We have identified a mechanism that enhances the ability of regulatory T cells to put the brakes on the immune response in tumors but plays no role in immune system maintenance. For the first time, we may now have an opportunity to selectively target the activity of regulatory T cells for treatment of cancer without inducing autoimmune or inflammatory complications."

The mechanism is built around two proteins. One, semaphorin-4a (Sema4a), is carried on the surface of various immune cells that can spark inflammation. The other, neuropilin-1 (Nrp1), is carried on the surface of regulatory T cells.

Vignali and his colleagues used a variety of molecular and cellular techniques to show that Sema4a binding to Nrp1 turns on a biochemical pathway in mouse regulatory T cells that enhances their function, stability and survival. When scientists eliminated Nrp1 on just regulatory T cells, those cells were unable to respond to signals that normally bolstered their anti-inflammatory activity.

When investigators analyzed human regulatory T cells, they found evidence that the pathway may also serve the same role.

In addition, more than 16 months after losing Nrp1 activity in their regulatory T cells, the mice showed no signs of autoimmune or inflammatory complications. "That is significant because mice and humans that lack or have substantial defects in regulatory T cells develop lethal autoimmune disease," Vignali said.

Knocking out or blocking the activity of Nrp1 on regulatory T cells in mouse models of several human cancers, including the deadly skin cancer melanoma, led to reduced, delayed or complete elimination of the tumors. Blocking Sema4a had a similar anti-tumor effect, researchers reported. "The

impact was particularly dramatic in a mouse model of human melanoma," Vignali said. "Mice lacking Nrp1 on regulatory T cells were almost completely resistant to developing melanoma, but did not develop any autoimmune or inflammatory complications."

Although investigators have not yet identified which cells carry Sema4a in tumors and boost regulatory T cell function, the scientists did report that immune cells called plasmacytoid dendritic cells (pDCs) provided more than half of the Sema4a in tumors in this study. That was surprising because pDCs make up a very small percentage of immune cells, and there is a long history of suppressive interactions between regulatory T cells and pDCs in tumors, Vignali said. Both cell types are recognized as inducing the immune system to tolerate, rather than attack, tumors.

Researchers also provided new details of how the Nrp1 pathway functions, including evidence that along with bolstering the ability of regulatory T cells to suppress the immune response, the pathway also helps maintain a stable population of regulatory T cells. "This pathway does not just boost regulatory function. It may define how regulatory T cells maintain their identity," said Greg Delgoffe, Ph.D., a postdoctoral fellow in Vignali's laboratory. Delgoffe and Seng-Ryong Woo, Ph.D., a former postdoctoral fellow in Vignali's laboratory, are co-first authors.

More information: Stability and function of regulatory T cells is maintained by a neuropilin-1–semaphorin-4a axis, DOI: 10.1038/nature12428

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