Tumor suppressor protein plays key role in maintaining immune balance

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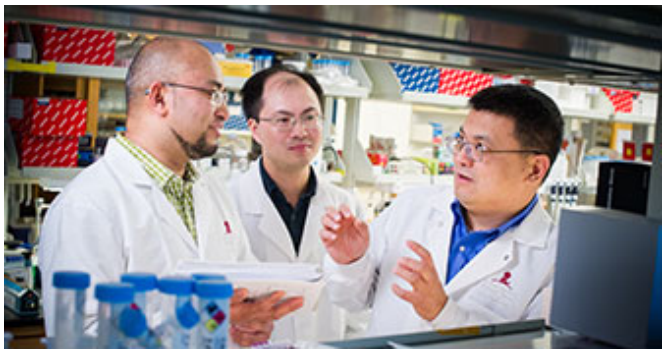

St. Jude Children's Research Hospital scientists have discovered that a protein widely known for suppressing tumor formation also helps prevent autoimmune diseases and other problems by putting the brakes on the immune response. The research was published recently online ahead of print in the scientific journal *Nature Immunology*.

Researchers showed that the tumor suppressor protein PTEN is essential for proper functioning of regulatory T cells. This small population of white blood cells helps to maintain immune system balance by suppressing specialized T cells called helper T cells that fuel distinct parts of the immune response. The helper T cells investigated in this study included type 1 T helper (Th1) and follicular T helper (Tfh) cells.

The interplay between regulatory T cells and helper T cells is crucial for both combating infections and for preventing misguided immune attacks that lead to autoimmune diseases and other problems. But details of how regulatory T cells control the diverse functions of various helper T cells have been elusive. This study fills key gaps in that understanding, particularly PTEN's role. The work also identified a new focus for research to improve treatment of autoimmune diseases.

PTEN is best known as one of the most frequently altered tumor suppressor genes in human cancers, but loss of the protein has also been tied to autoimmune problems. This study showed that is because PTEN is required to maintain the stable population of regulatory T cells that keeps the immune system in check.

"In humans we know that loss of PTEN leads to tumors. This study highlights another role and shows that PTEN is also crucial for proper functioning of regulatory T cells and prevention of autoimmune diseases," said corresponding author Hongbo Chi, Ph.D., a member of the St. Jude Department of Immunology. "In mice, the loss of just one copy of the PTEN gene in regulatory T cells is sufficient to set the stage for autoimmune problems."

Working in specially bred mice, researchers showed that deleting the PTEN gene in regulatory T cells was followed by a dramatic increase in the number of Tfh and related cells. Tfh cells aid production of antibodies, which combat infections. But when produced inappropriately, antibodies can also drive autoimmune disorders like lupus. The mice in this study developed kidney damage and immune changes associated with lupus. Restoring PTEN to 50 percent of normal levels did not protect the mice from inflammatory disease.

Researchers found evidence that Th1 cells influence the activity of Tfh cells. Th1 cells produce the chemical messenger interferon gamma that revs up the immune response. When researchers blocked interferon gamma production in the specially bred mice, the number of Tfh cells fell along with lupus-like immune abnormalities.

"We have identified a crucial role of PTEN in controlling Tfh cells and autoantibody production. Additionally, by linking the role of PTEN to Tfh cells,

we have opened doors for further investigation of Tfh related lymphomas," said co-first author Sharad Shrestha, a graduate student in Chi's laboratory. Added co-first author Kai Yang, Ph.D., a staff scientist in Chi's laboratory: "These results reveal a hierarchy of control that regulatory T cells use to simultaneously regulate Th1 and Tfh cells. We showed that Th1 production of interferon gamma is a pre-requisite for the activity of Tfh cells."

The findings also yielded insight into a cell signaling pathway that regulates many important functions, including T cell activity, in response to changing conditions. This is the mTOR pathway, in which the protein complexes mTORC1 and mTORC2 play central roles.

Investigators showed that deletion of PTEN in regulatory T cells led to increased activity of mTORC2 but not mTORC1. When scientists blocked mTORC2 activity in mice whose regulatory T cells lacked PTEN, immune system balance and activity returned to normal. "Our research establishes that the interaction of PTEN and mTORC2 functions as a central pathway to maintain the stability of the regulatory T cell population and to ensure their ability to control the activity of Th1 and Tfh cells," Chi said. The newly identified PTEN-mTORC2 axis provides another target for efforts to develop better treatments of autoimmune and other disorders.

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