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Tumor suppressor protein is a key regulator of immune response and balance

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St. Jude Children's Research Hospital scientists have identified a key immune system regulator, a protein that serves as a gatekeeper in the white blood cells that produce the "troops" to battle specific infections.

Researchers demonstrated the protein, Tsc1, is pivotal for maintaining a balanced immune system and combating infections. Loss of the Tsc1 protein was associated with a reduction in the number of certain immune cells and a weaker immune response. The work appears in the July 17 online edition of the scientific journal Nature Immunology.

Scientists found that Tsc1 works by inhibiting the pathway that launches production of the specialized white blood cells known as effector T cells. Those cells are the backbone of the adaptive immune response, designed to respond, identify and destroy specific bacteria, viruses and other threats.

Working in mice with specially engineered immune systems, scientists showed Tsc1 also keeps cellular activity at a minimum in the white blood cells known as naïve T cells. That process is known as quiescence.

Quiescence has long been recognized as crucial to proper immune function. But until now scientists were unclear how quiescence was established and maintained in naïve T cells. "This study is the first to show that Tsc1 is a primary regulator of T cell quiescence," said Hongbo Chi, Ph.D., assistant member St. Jude Department of Immunology, and the study's senior author. The first author is Kai Yang, Ph.D., a

postdoctoral fellow in Chi's laboratory.

"These findings not only advance understanding of the cell biology of the immune system but also have great potential for clinical applications in the future," Chi said. He speculated that the same process might also be important in regulating immune cells known as memory T cells that help the immune system recognize infectious agents encountered before and mount a rapid immune response.

Tsc1 is best known as a tumor suppressor, helping to prevent cancer development by inhibiting activity of the mTOR protein and the pathway that bears its name. The mTOR pathway plays a key role in cancer, metabolic disease and aging.

Now Chi and his colleagues demonstrated that in the immune system Tsc1 has a unique job. Through inhibition of the mTOR pathway, Tsc1 forces naïve T cells to maintain minimal metabolic and cellular activity. Normally that would only change when naïve T cells are activated and begin producing the more specialized effector T cells to combat a specific new threat.

In this study, scientists showed that loss of the Tsc1 protein predisposed affected T cells to premature activation, resulting in programmed cell death via the cell's suicide pathway. Consequently, the process depleted the supply of T cells as well as another group of specialized immune cells known as invariant natural killer T cells. The loss also dampened the ability of mice to combat bacterial infections. "We think maintaining T cell quiescence is central to preventing premature cell death and ensuring a productive immune response," Chi said.

Although more work is needed to understand mTOR regulation of T cell quiescence, this study offers a glimpse into the process. Tsc1 is part of a larger complex known to regulate mTOR activity. The mTOR protein is

also a component in two larger complexes, known as mTORC1 and mTORC2. Chi and his colleagues demonstrated that naïve T cell quiescence requires Tsc1 to keep mTORC1 activity at a low level. If Tsc1 is lost or shut down prematurely, mTORC1 activity increases, leading to premature activation of the immune cells, which results in various abnormalities and cell death.

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