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Researchers discover how a protein complex revs up T cell activation to fight infections

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St. Jude Children's Research Hospital scientists have identified a protein complex that is essential for jumpstarting the immune response during the critical first 24 hours of an infection. The research appears in the current issue of the scientific journal *Immunity*.

Researchers showed the protein complex mTORC1 helps to ensure that newly activated T cells have the energy necessary to launch proliferation. T cells are white blood cells that fight disease and promote immune system balance. An effective immune response depends on proliferation for rapid production of an army of T cells that can recognize and eliminate infectious threats.

Investigators also showed that mTORC1 works through glucose metabolism to affect the supply of more specialized T cells, including T helper 2 (Th2) cells. Th2 cells fight parasites, but also fuel asthma-associated lung inflammation.

The work answers important questions about the first 24 hours of an immune response when T cells transition from a quiescent or resting state and are activated to fight infections. "We show that mTORC1 is required for T cells to exit quiescence and begin proliferation. We have also found that the complex plays a role in production of Th2 cells," said corresponding author Hongbo Chi, Ph.D., an associate member of the St. Jude Department of Immunology. The first author is Kai Yang, Ph.D. a postdoctoral fellow in Chi's laboratory.

The findings also highlight possible strategies for restoring immune balance by easing the inflammation of asthma or autoimmune disorders. The mTORC1 complex is already targeted by the immune suppressive drug rapamycin. "Our data show that T cell metabolism, which is orchestrated by mTORC1, could also be targeted for therapeutic benefit in the treatment of asthma and other diseases in which particular metabolic pathways play a role," Chi said.

In this study, researchers used specially bred mice to identify mTORC1's role in T cell activation and proliferation. Investigators began by deleting the signature protein of either mTORC1 or the related mTORC2 complex in mouse T cells. The scientists then tracked how those T cells functioned compared to normal T cells. The mTORC1 deletions involved a protein named Raptor.

The results showed that mTORC1 functions as the middleman to prime T cells to begin producing massive numbers of white blood cells to combat a particular infectious agent. The complex responds to signals from immune receptors on the cell surface by increasing the activity of genes involved in glucose and lipid metabolism. Stimulation and signaling by the T cell receptor and other immune receptors like the CD28 molecule mark the start of T cell activation, but until this study little was known about how T cells completed the process and began proliferation.

Researchers also showed that signaling from both the T cell receptor and CD28 was required to sustain mTORC1 activity. "The results points to the unexpected importance of CD28 signaling in the process," Yang said.

That was not the only surprise. While mTORC1 was required to launch proliferation, after 24 hours the complex was not essential for continued T cell production. "That suggests that the first 24 hours of T cell activation are the most metabolically demanding and require the most

robust mTORC1 activity," Chi said.

Previous studies demonstrated that mTORC1 is required for T cells to differentiate and take on the more specialized roles of T helper 1 or T helper 17 cells. This study showed that Th2 cells also depend on mTORC1 in its role as coordinator of glucose metabolism. Glucose metabolism affects the ability of T cells to respond to the particular chemical messengers, or cytokines, that promote production of Th2 cells.

Investigators showed that deleting Raptor or blocking glucose metabolism also inhibited production of Th2 cells. Based on the results, Chi said he could envision an asthma treatment that worked by lowering glucose metabolism in T cells to reduce the population Th2 cells that cause lung inflammation. The same principle could apply to other inflammatory diseases like arthritis and colitis.

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