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Scientists find protein that reins in runaway network

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Marked for death with molecular tags that act like a homing signal for a cell's protein-destroying machinery, a pivotal enzyme is rescued by another molecule that sweeps the telltale targets off in the nick of time.

The enzyme, called TRAF3, lives on to control a molecular network that's implicated in a variety of immune system-related diseases if left to its own devices.

The University of Texas MD Anderson scientists identified TRAF3's savior and demonstrated how it works in a paper published online Sunday in *Nature*.

By discovering the role of OTUD7B as TRAF3's protector, Shao-Cong Sun, Ph.D., professor in MD Anderson's Department of Immunology, and colleagues filled an important gap in their understanding of a molecular pathway discovered in Sun's lab.

"Genetic defects or constant degradation of TRAF3 lead to the uncontrolled activity of what we call the non-canonical NF-kB pathway. This in turn, is associated with autoimmune diseases and lymphoid malignancies such as multiple myeloma and B cell lymphomas," Sun said. "Understanding how the degradation of TRAF3 is regulated is extremely important."

Dodging annihilation, turning the tables

Sun earlier found an alternative, or non-canonical, pathway that activates the protein complex known as NF-kB, a family of proteins that turns on genes that are important in immune response, inflammation, cell growth and survival, and development.

They found that NF-kB activity increases when TRAF3 has the homing targets, called ubiquitins, attached to it and is destroyed by the proteasome, a complex of proteins that hunts down ubiquitin-decorated proteins.

When TRAF3 evades attack, it turns that same destructive mechanism against NIK, a protein that's central to NF-kB activity, by tagging it with ubiquitins.

The key question was: What regulates TRAF3's destruction and, in the process, controls NF-kB?

OTUD7B emerges

Sun and colleagues had a candidate, the enzyme OTUD7B, also known by its more lyrical name, Cezanne. It was genetically quite similar to another enzyme active in the canonical pathway for NF-kB called A20. Both were known deubiquitinases, enzymes that cleave ubiquitin polymers. A20 is not active in the non-canonical NFkB pathway.

By applying inducers of the non-canonical NK-kB pathway to cells derived from OTUD7B-deficient mice, the researchers found:

- Degradation of TRAF3 and accumulation of its target, NIK
- Ubiquitination of TRAF3

Cells with OTUD7B intact suppressed non-canonical NF-kB signaling.

Varied immune effects in mice

Knocking out the OTUD7B gene caused biological changes in mice, but it did not kill them, as occurs when A20 is knocked out.

Mice with OTUD7B suppressed had greatly increased lymphoid cell growth in the lining of the intestine and hyper-responsiveness to antigens by B cells. "If these two symptoms occur persistently, as they did in the knockout mice, they may contribute to autoimmunity or inflammation," Sun said.

However, knockout mice also had an improved immune response to the lethal intestinal bacterial pathogen C. rodentium. All of the mice with normal OTUD7B died of the bacterial infection, while 75 percent of the knockout mice survived.

Teasing out the reasons for these effects and developing OTUD7B as a target for inhibitors to boost immunity in the lining of the intestine will take more research, Sun said.

"It's important to know that TRAF3 has opposing roles in regulating activation of T cells and B cells, indicating that OTUD7B has a cell-type specific function. So, as with many other research findings, it might take considerably more effort to assess the therapeutic potential of OTUD7B," Sun said.

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