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# Team discovers new player critical to unleashing T cells against disease

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A major study from researchers at the La Jolla Institute for Allergy and Immunology provides new revelations about the intricate pathways involved in turning on T cells, the body's most important disease-fighting cells, and was published today in the prestigious scientific journal *Nature*.

The La Jolla Institute team is the first to prove that a certain type of protein, called septins, play a critical role in activating a calcium channel on the surface of the T cell. The channel is the portal through which calcium enters T cells from the blood stream, an action essential for the T cell's survival, activation, and ability to fight disease.

Patrick Hogan and Anjana Rao, Ph.D.s, are senior authors on the paper and Sonia Sharma and Ariel Quintana, Ph.D.s, are co-first authors. Drs. Sharma, Rao and Hogan are former researchers at Harvard Medical School with high-level genetics expertise who joined the La Jolla Institute in 2010. Dr. Quintana conducted advanced microscopy that was a major aspect of the study.

Dr. Hogan describes the discovery as another important step in understanding the overall functioning of T cells – knowledge from which new, more precisely targeted drugs to treat diseases ranging from cancer to viral infections can emerge. "It's like working on an engine, you have to know what all the parts are doing to repair it," he says. "We want to understand the basic machinery inside a T cell. This will enable us to target the specific pressure points to turn up a T cell response against a

tumor or virus or to turn it down in the case of autoimmune diseases."

The findings were published in a *Nature* paper entitled "An siRNA screen for NFAT activation identifies septins as coordinators of store-operated Ca2+ entry."

"We have found that the septin protein is a very strong regulator of the calcium response, which is essential for activating immune cells," says Dr. Sharma, who was recently appointed to a faculty position, and now leads her own independent laboratory at the La Jolla Institute, in addition to serving as scientific director of the newly established RNAi screening center.

Dr. Hogan says the discovery took the research team by surprise. "We knew septins existed in the cellular plasma (surface) membrane, but we didn't know they had anything to do with calcium signaling," he says. Septins are known to build scaffolding to provide structural support during cell division.

This finding builds on Dr. Rao and Dr. Hogan's groundbreaking discovery in 2006 showing that the protein ORAI1 forms the pore of the calcium channel. The channel's entryway had been one of the most sought after mysteries in biomedical science because it is the gateway to T cell functioning and, consequently, to better understanding how the body uses these cells to fight disease.

To the research team's surprise, the septins were forming a ring around the calcium channel. "We aren't sure why, but we theorize that the septins are rearranging the cellular membrane's structure to "corral" the key proteins STIM and ORAI1, and maybe other factors needed for the calcium channel to operate," says Dr. Hogan.

Dr. Sharma adds that, "essentially we believe the septins are

choreographing the interaction of these two proteins that are important in instigating the immune response." Without the septins' involvement, T cell activation does not occur.

In the study, the researchers devised a simple visual readout of activity in a main pathway responsible for activation of T cells— the same pathway that is targeted by the immunosuppressive drug cyclosporin A that is used clinically—and looked for impairment of the activity when individual genes were, in effect, deleted. After sorting through the roughly 20,000 human genes, they turned up 887 gene "hits," says Dr. Hogan.

With further experiments, they should be able to classify those hits into genes that affect the calcium channel itself and genes that act later in the pathway. "We are hopeful that one or more of these genes can be used as a clinical target for new drugs to treat transplant rejection and immune diseases, some of the same indications now treated with cyclosporine A," adds Dr. Hogan. He believes that a medication aimed at an early step of calcium entry through the ORAI channel could be more effective and have fewer side effects than cyclosporin A, which targets a later step in the pathway and can cause complications such as kidney disease.

**More information:** An siRNA screen for NFAT activation identifies septins as coordinators of store-operated $Ca^{2+}$ entry, DOI: 10.1038/nature12229

Provided by La Jolla Institute for Allergy and Immunology

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