fast breaking papers - 2010

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Ricardo Dolmetsch talks with *ScienceWatch.com* and answers a few questions about this month's Fast Breaking Paper Paper in the field of Molecular Biology & Genetics.

Article Title: STIM1 Clusters and Activates CRAC Channels via Direct Binding of a Cytosolic Domain to Orai1
Authors: Park, CY;Hoover, PJ;Mullins, FM;Bachhawat, P;Covington, ED; Raunser, S;Walz, T;Garcia, KC;**Dolmetsch, RE**;Lewis, RS
Journal: CELL, Volume: 136, Issue: 5, Page: 876-890, Year: MAR 6 2009
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(addresses have been truncated.)

SW: Why do you think your paper is highly cited? Does it describe a new discovery, methodology, or synthesis of knowledge?

Store-operated calcium channels (SOC) are critically important for many biological processes, including activation of the immune system, activation of platelets, and repair of muscle cells. These channels are formed by Orai, which is an ion channel at the cell membrane, and Stim, which is an ER protein that contains a calcium-biding domain in the ER lumen and a cytoplasmic domain.

The mechanism by which Stim activates Orai had been very controversial with different groups proposing that Stim generates a second messenger, that it recruits other proteins that bind to Orai and that it catalyzes the formation of Orai pores by dimerizing existing Orai dimers.

Our paper went a long way towards resolving these controversies by showing that Stim activates Orai by binding directly. We identified the key domains of both Stim and Orai that bind to each other, and used a variety of independent approaches to show that this binding is direct and is necessary and sufficient for activation of Orai.

In addition, we demonstrated that the critical domain of Stim (which we call the CRAC Activation Domain or CAD) can multimerize Orai channels both *in vitro* and *in vivo* but that this multimerization step is not required for channel activation.

In summary, our paper describes a key set of discoveries that contribute significantly to our understanding of how SOCs work in cells and it also resolves some of the questions surrounding how Stim activates Orai and provides a rough mechanism to explain how this happens in cells.

"I think that this paper will greatly accelerate the development of small molecules that can activate or inhibit Orai and Stim and which will allow us to treat auto-immune disease in ways that are not possible today."

SW: Would you summarize the significance of your paper in layman's terms?

T cells are cells of the immune system that are critical for preventing infection and cancer but can also cause autoimmune diseases like multiple type 1 diabetes mellitus and multiple sclerosis. Calcium is an important signaling molecule in these cells and therefore the proteins that control calcium signals are essential for the function of the immune system. Among the most important of these are proteins called calcium channels, which carry calcium from the blood into immune cells and regulate biochemical processes that are required to mount an immune response.

In this paper, we studied a calcium channel called Orai, which is the most important calcium channel in immune cells and is absolutely necessary for activation of the immune response. Patients that have mutations in Orai are severely immunodeficient and are subject to severe life-threatening infections. By using a series of biochemical and cell biological techniques, we discovered that Orai channels are activated by the direct binding of another protein called Stim.

We found that Stim binds directly to Orai and causes it to change its shape, allowing calcium into cells. In the process we identified key regions of both Orai and Stim that interact with each other. This new knowledge is now helping us develop drugs that target Stim and Orai and that can be used to control the activation of the immune system in the context of autoimmune disease cancer and other disorders.

SW: How did you become involved in this research, and were there any problems along the way?

I have long been interested in understanding how calcium channels control the development of cells in the immune system and nervous system. In my lab, Dr. Chan Young Park developed many biochemical and genetic tools to study calcium channels and we became interested in using them to study SOCs. My colleague Richard Lewis is one of the world's experts on SOCs and he has made some of the most important discoveries in this field. Together, we formed a very effective partnership that allowed us to combine our biochemical techniques with Rich's experience measuring these channels in cells.

There were many problems along the way and there are still many things we do not understand, but overall, this paper provides clear evidence for how a successful collaboration can be greater than the sum of its parts.

SW: Where do you see your research leading in the future?

We continue to work on several aspects of Orai and Stim biology, both using our knowledge to develop inhibitors and activators of this pathway in studying how Stim interacts with other proteins. Rich Lewis has a number of exciting findings that provide greater insight into how this molecular machine is controlled. This promises to be a very exciting field for many years to come.

Do you foresee any social or political implications for your research?

I think that this paper will greatly accelerate the development of small molecules that can activate or inhibit Orai and Stim and which will allow us to treat autoimmune disease in ways that are not possible today.

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