FAST BREAKING PAPERS - 2008

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PDF

David L. Armstrong & Lutz Birnbaumer talk with *ScienceWatch.com* and answer a few questions about this month's Fast Breaking Paper in the Multidisciplinary field .

Article Title: Orai proteins interact with TRPC channels and confer responsiveness to store depletion
Authors: Liao, Y;Erxleben, C;Yildirim, E;Abramowitz, J;Armstrong, DL; Birnbaumer, L
Journal: PROC NAT ACAD SCI USA
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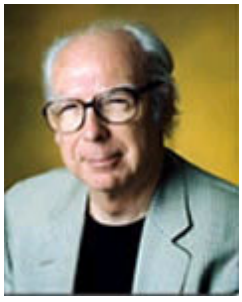
(addresses have been truncated)

SW: Why do you think your paper is highly cited?

Because it unifies two independent lines of research into the identity of the ion channel proteins that are responsible for calcium entry into cells in response to G protein-mediated depletion of intracellular calcium stores.

One line of research, which originated from studies of fruit fly vision, implicated TRPC channels as the mediators of store-operated calcium entry. A second more recent line of research, which involved genetic screens of calcium entry in the *Drosophila* Schneider (S2) cell line, implicated Orai proteins in store-operated entry, even though Orai proteins have different secondary structure than any previously identified ion channels.



Nevertheless, mutations in Orai proteins that produced immunodeficiency in humans were shown to block store-operated entry in lymphocytes (Patrick G. Hogan and Anjana Rao, "Dissecting I_{CRAC}, a store-operated calcium current," *Trends Biochem. Sci*. 32:235-45, 2007). Our study provided some of the earliest evidence, and an unambiguous summary of the hypothesis in Fig. 5, that the two classes of protein could act synergistically to mediate calcium entry.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

Our paper describes a new discovery that resulted when we carried out a classic experiment somewhat differently than previous investigators. By restricting expression of both TRPC and Orai proteins, we observed a

synergy that had not been reported previously, although there were already examples in the literature of accessory proteins affecting the properties of other ion channel proteins.

Coauthor
Lutz Birnbaumer

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

Calcium ions trigger many of the fundamental cellular processes on which human health depends, but too much calcium is toxic to cells, so cells sequester calcium ions in intracellular organelles and strictly regulate their release. Many proteins are involved in regulating calcium entry into the cell, but, until recently, one of the most mysterious proteins was the one mediating calcium entry in response to depletion of intracellular calcium stores. Without this entry from outside, cells would exhaust their calcium stores and stop signaling. Knowing what proteins are responsible for entry provides a therapeutic target for diseases that involve disruption of calcium signaling.

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

Dr. Lutz Birnbaumer has been studying G protein-dependent signaling since he was a postdoctoral fellow at NIH in the lab of Martin Rodbell, who won the Nobel Prize in medicine in 1994 with Alfred Gilman for their discovery of G proteins (See: Birnbaumer L, "Expansion of signal transduction by G proteins. The second 15 years or so: from 3 to 16 a subunits plus ß? dimmers," *Biochim. Biophys. Acta*. 1768:756–71, 2007).

Many years later, Dr. Birnbaumer's own student, Ching-Fong Liao, at the Baylor College of Medicine, discovered that G protein-coupled M5 muscarinic receptors stimulate the enzyme phospholipase C (PLC) which hydrolyses membrane phospholipids and triggers both the initial release of calcium from stores and the subsequent calcium entry.

At the same time Israeli scientists had postulated that an ion channel protein in flies, called "transient receptor potential" or TRP, because of the effects of mutating it on phototransduction, which also depends on signaling through phospholipase C, might be the mysterious calcium channel responsible for store-operated calcium entry into mammalian cells.

"Calcium ions trigger many of the fundamental cellular processes on which human health depends, but too much calcium is toxic to cells, so cells sequester calcium ions in intracellular organelles and strictly regulate their release."

Therefore, Dr. Birnbaumer and his postdoctoral fellow, Michael Xi Zhu, set out to identify the mammalian orthologue of TRP. They discovered that mammals express a large family of TRP proteins (See: Xi Zhu *et al*., "*trp*, a novel mammalian gene family essential for agonist-activated capacitative Ca^{2+} entry," *Cell* 85:661-71, 1996), which were subsequently named TRPC to reflect their close homology with the canonical TRP from *Drososphila*.

However, when the TRPC proteins were expressed heterologously, they did not show the calcium selectivity that was predicted from electrophysiological studies of native store-operated channels. Nevertheless, in the absence of other plausible candidates, TRPCs became the focus of many people in the field, and there were numerous reports from many laboratories with indirect evidence implicating TRPC channels in store-operated calcium entry. It was somewhat surprising, therefore, that any role for TRPC proteins disappeared when Orai was discovered (Taylor CW, "Store-operated Ca(2+) entry: a STIMulating stOrai" *Trends Biochem. Sci.* 31: 597–601, 2006). The study reported by Liao *et al*. (see below) was an attempt to reconcile these two disparate lines of research.

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

Earlier this year we published a second paper (Y Liao *et al.,* "Functional interactions among Orai1, TRPCs, and STIM1 suggest a STIM-regulated heteromeric Orai/TRPC model for SOCE/Icrac channels," *Proc. Natl. Acad. Sci. USA* 105: 2895-2900, 2008) that provides additional electrophysiological evidence for the participation of TRPC proteins in Orai-dependent, store-operated calcium entry in human embryonic kidney (HEK) cells.

This paper also has new genetic evidence that mutants of Orai proteins, which are associated with immune disease, not only disrupt store-operated entry but also disrupt receptor-operated calcium entry, which, as more people already agree, also involves TRPC channels. Nevertheless, no one yet has been able to provide direct evidence for the structure of the channel or its function at the molecular level, so that is where our efforts are currently directed.

Now that the Human Genome Project has provided us with a catalogue of human proteins, many important areas of biological research are currently shifting from identifying proteins to understanding how they assemble and work together to carry out cellular processes.

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

The implications of our research are primarily in understanding human disease. Additional physiological roles for TRPC channels and Orai proteins in asthma, diabetes, hypertension, and psychiatric disorders are being discovered by many groups using mice which have specific genes deleted. On the other hand, the implications of our discovery for human health do illustrate how essential basic research support is to translational medicine, so in that sense it does have political implications for science funding.

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Keywords: TRPC and orai proteins, ion channel proteins, calcium entry into cells, TRPC channels, Drosophila Schneider, S2, cell line, restricting expression, Martin Rodbell, receptor-operated calcium entry, human embryonic kidney cells, HEK cells, translational medicine.

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