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A Monthly Forum for Johns Hopkins Medicine Faculty and Senior Staff
JOHNS HOPKINS MEDICINE
March 2008
Volume 12
Number 3

The Two Faces of Calmodulin

David Yue is delving into the mysteries of calcium channels.

Biomedical engineer David Yue and his team are tickled by their latest discovery, published this past Valentine's Day in the journal *Nature*. The topic of the letter, calcium signals, may not seem romantic, but everyone's heartbeat is propelled by the process. And that gushy feeling when you're in love? That too has to do with the supersonic flow of calcium ions telling those love-struck neurons to fire. Feeling like you can't breathe? Your diaphragm depends on calcium, too. But what's really got Yue's blood pumping is that his lab has discovered something that's so far remained elusive about calcium signals.

Many physiological responses stimulated by calcium ions come about because calcium introduced into the cell binds to the protein calmodulin (CaM). And the amount of calcium that enters a cell is moderated by calmodulin too. To facilitate this moderation, these sensor calmodulin molecules butt right up against the terminal segments of calcium channels. When a channel opens for just a millisecond, thousands of Ca^{2+} ions race into the cell. Calmodulin acts as a thermostat to provide a way for the channel to know that there's plenty of calcium and it's time to shut off, or there's not enough, and it's time to open the floodgates. The burning question for the past decade has been: How does CaM do its regulatory job since it's sensing a concentration of calcium just nanometers from the super-high-density inflow?

"The challenge is akin to that in a cocktail party," says Yue, whose team on the study includes graduate students Ivy Dick and Michael Tadross. Say the room is full of people. Everyone's talking at the same time, but you can choose to tune out all the background noise and hear the person right next to you ("local selectivity"). Alternatively, you can also choose to somehow tune out the loud nearby person and listen to the quiet conversation from way across the room ("global selectivity"). It's hard to believe that it could work, but for CaM, Yue says, it's true that a similar choice is made. In one sensing mode, CaM can hear a barrage of Ca^{2+} ions intense banter straight out of the channel, while in another mode CaM can switch its regulatory prowess

to get a read on the distant and weaker calcium signals from the rest of the cell.

Yue says that in digging into the mystery of how CaM manages this two-faced feat, his team discovered a small module on CaV1 and CaV2 calcium channels that switches the selectivity of CaM decoding between global and local extremes; this module enables different channel types to fine-tune spatial Ca2+ sensitivity. They named the module, NSCaTE, for N-terminal spatial Ca2 + transforming element, and this finding was reported in their recent *Nature* letter. Yue says that the long-sought-after mechanistic secret of local/global Ca2+ selectivity is contained within NSCaTE, and a full account of this vital secret will soon be reported in another paper currently under review.

Because many diseases result when calcium channels are not properly switched on or off, Yue says that knowing how calmodulin moderates these channels is of vital medical importance. And to give him an even greater stab at figuring out the moderating mechanisms, Yue and postdoctoral fellow Masayuki Mori, turned to biophysicist Dan Leahy, whose lab looks at the crystallographic structures of proteins.

Under the tutelage of Leahy and his postdoctoral fellow Craig Vander Kooi, Yue and Mori were able to take a molecular picture of calmodulin and see where the protein binds to the switch region of the calcium channel—the point that can flip the channel on and off. They looked at two specific calcium channels, CaV2.1 and CaV2.3, that are of major interest to Yue. What they uncovered is an atom-by-atom picture of how calmodulin interacts with the channel switch. The dumbbell structure of calmodulin essentially folds up and engulfs the switch module. “Basically what we’re doing is providing a molecular picture of the interaction to interpret baseline physiological effects,” says Leahy. This work was reported in the April 2008 issue of the journal *Structure*.

For Yue, the ongoing mysteries between calcium and calmodulin are pure poetry. “Most people think milk and strong bones when they think of calcium,” he says. “But it’s so much more.” ■

—Victoria Bruce

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