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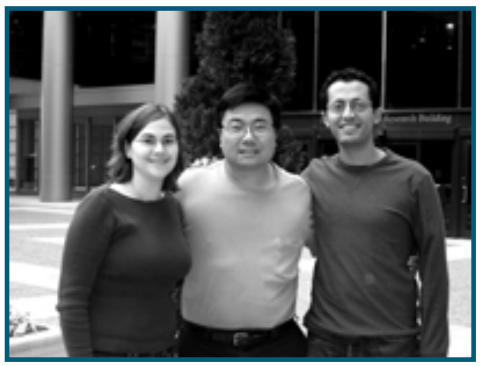
Opinions

David Yue explains the past—and promises—of calcium signal research



BASICS: One of your discoveries was such a boon that you dubbed it "The Rosetta Stone." Why?

YUE: Yes, we call NSCaTE the Rosetta Stone. The existence and crucial importance of local/global Ca2+ selectivity have been recognized now for nearly a decade, but the underlying mechanism of this selectivity has been elusive. NSCaTE provides a vital and practical clue by which the mechanism could be unlocked, much as the Rosetta Stone ultimately enabled translation of Egyptian hieroglyphics.

BASICS: You've likened your recent research on calcium signals to a trilogy with the first advance being the discovery of NSCaTE. What are the second and third parts?

YUE: The second advance uses novel experimental means to control Ca2+ concentrations within nanometers of channels, and thereby uncovers a deep mechanism of spatial Ca2+ selectivity, as conveyed by NSCaTE. Stay tuned, this story is coming out soon.

The third result of the trilogy is the atomic resolution of calmodulin in complex with a vital element of neuronal Ca2+ channels. Obtained in collaboration with Daniel Leahy's group, this structure suggests some unanticipated atomic-level conformational changes that underlie CaM decoding of Ca2+ concentrations. These results provide a molecular-structural context for parts one and two of the trilogy, and just came out in the April 2008 issue of the journal Structure, with postdoctoral fellow Masayuki Mori as the lead author.

BASICS: What are some of the future promises of calcium signal research?

YUE: Ca2+ is one of the main languages of life at the molecular and cellular levels. Understanding how this language is encoded and decoded promises understanding of normal biological function, as well as disease processes. Identifying molecular manipulations that can tune Ca2+ signaling has huge potential for developing therapies for a wide spectrum of diseases. For example, heritable problems in Ca2+ feedback regulation of Ca2+ channels in Timothy Syndrome are implicated in autism, cardiac arrhythmias, and faulty development. How this syndrome arises, and how to ameliorate the consequences of this disease, is intimately related to

Ca2+ signal research. ■

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