PROGRESS IN NEUROSCIENCE PINS

Seminar Series of the
Brain & Mind Research Institute
Weill Cornell Medical College (WCMC)
&
The Graduate Program in Neuroscience of
WCMC and Sloan Kettering Institute

Thursday, 3/31/16, 4 PM, coffee at 3:45 PM
Weill Auditorium

"Local and Long-Range Signaling in Neurons: Mechanisms and Implications for Disease"

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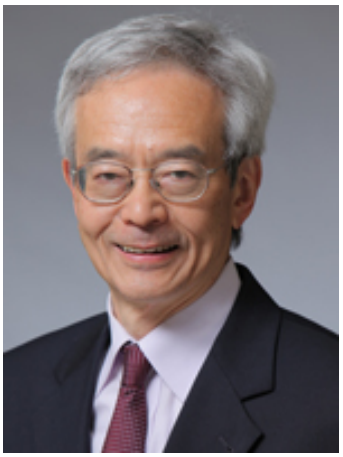

Abstract:

The primary language of excitable cells (action potential firing) is converted into the primary language of intracellular activity (biochemical signaling) by voltage-gated Ca^{2+} channels (Ca_Vs). This occurs in excitation-contraction (E-C) coupling and excitation-secretion (E-S) coupling. *Excitation-transcription* (E-T) coupling is more general, yet less understood. A subfamily of Ca_Vs, Ca_V1 (L-type) channels, are essential for excitation-transcription coupling to nuclear CREB, a transcription factor critical in learning and memory. However, even the earliest step in this signaling is not fully understood. Local Ca^{2+} elevations near the Ca_V1 channels help trigger the signaling cascade, but these channels could also convey a voltage-dependent conformational signal (VCS), like the conformational signal in E-C coupling. We have devised an approach whereby conformational changes required to open the Ca_V pore are experimentally decoupled from Ca^{2+} influx into the channel nanodomain. This dissection uncovered a remarkable joint requirement for both Ca^{2+} flux and voltage-dependent conformational changes in excitation-transcription coupling. Thus, Ca_V1 signaling to CREB behaves as an AND gate. The key local signaling intermediate is a cluster of α- and βCaMKII molecules.

Another puzzle is how local signaling at Ca_V1 channels is relayed onward to the nucleus. We have discovered a novel mechanism that mediates long-distance communication: a shuttle that transports Ca^{2+}/calmodulin from the surface membrane to the nucleus. The shuttle protein is yet another CaMKII isoform, γCaMKII. Its phosphorylation at Thr287 by βCaMKII protects the Ca^{2+}/CaM signal, and calcineurin (CaN) triggers its nuclear translocation. Both βCaMKII and CaN act in close proximity to Ca_V1 channels, supporting their dominance, while γCaMKII operates as a carrier, not as a kinase. Upon arrival within the nucleus, Ca^{2+}/CaM activates CaMKK and its substrate CaMKIV, the final CREB kinase. The significance of the mechanism is emphasized by dysregulation of Ca_V1, γCaMKII, αCaMKII, βCaMKII and CaN in multiple neuropsychiatric disorders including autism and schizophrenia.

Recent relevant publications:

1. Li B, Tadross MR, Tsien RW. Sequential ionic and conformational signaling by calcium channels drives neuronal gene expression. Science 2016 Feb 19; 351(6275):863-7. PMID 26912895
2. Ma H, Groth RD, Cohen S, Emery JF, Li B, Hoedt E, Zhang G, Neubert TA, Tsien RW (2014). γCaMKII shuttles Ca2+/CaM to the nucleus to trigger CREB phosphorylation and gene expression. Cell 2014 Oct 9; 159(2):281-94. PMID: 25303525.
3. Mullins C, Fishell G, Tsien RW. Unifying views of autism spectrum disorders: a consideration of autoregulatory feedback loops. Neuron in press

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