UC DAVIS HEALTH | SCHOOL OF MEDICINE

Department of
Physiology and Membrane Biology

Distinguished Lecture Series in Physiology

Scott Earley, Ph.D.

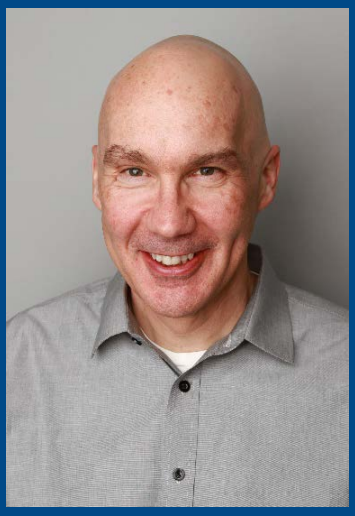
Professor
Department of Pharmacology
University of Nevada, Reno
School of Medicine

"An Unexpected Alliance: Vascular Function is Controlled by Nanoscale Association of TRPML1 Channels and Ryanodine Receptors"

Members of the transient receptor potential (TRP) superfamily of cation channels are found throughout the body and are critically involved in many aspects of physiology. TRPML1 (TRP mucolipin 1) is a Ca2+-permeable, non-selective cation channel that is localized to the membranes of endosomes and lysosomes (collectively referred to as endolysosomes) and is not abundant on the plasma membrane. Prior studies have shown that TRPML1 is vital for trafficking, intraluminal acidification, and other canonical functions of endolysosomes. We recently investigated the function of TRPML1 channels in fully differentiated vascular smooth muscle cells. Using a combination of live-cell confocal microscopy and super-resolution microscopy, we found that TRPML1 channels form a stable, nanoscale Ca2+ signaling complex with type 2 ryanodine receptors (RyR2) on the sarcoplasmic reticulum (SR). We also found that spontaneous Ca2+ signals resulting from release of Ca2+ from the SR through RyR2s ("Ca2+ sparks") and corresponding activation of large-conductance Ca2+-activated K+ were essentially absent in SMCs from TRPML1-knockout (Mcoln1-/-) mice. Using ex vivo pressure myography, we found that loss of this critical signaling cascade greatly exaggerated the vasoconstrictor responses of resistance arteries. Using in vivo radiotelemetry to record blood pressure, we found that showed that Mcoln1-/- mice are spontaneously hypertensive. We conclude that Ca2+ release from endolysosomes through TRPML1 channels initiates Ca2+ sparks, and that this process is critically important for the regulation of arterial contractility, vascular resistance, and blood pressure.

Thursday, October 17, 2019
GBSF Auditorium
4:00 p.m.

October 17



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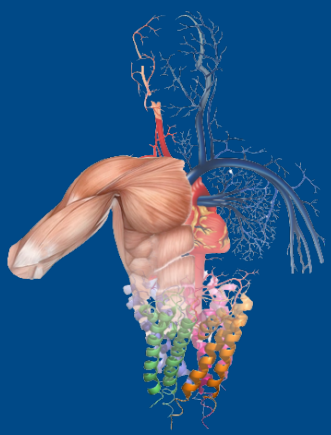

Host: Fernando Santana
lfsantana@ucdavis.edu