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STIM- Dependent calcium signaling mediate smooth muscle and cardiac cell growth

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Abstract

Stromal interaction molecules (STIM1 and STIM2) function as powerful sarcoplasmic (SR) Ca2+ sensors. When the SR Ca2+ content decreases STIM proteins migrate in proximity of the plasma membrane to activate the Orai channels initiating the so called Store Operated Ca2+ Entry (SOCE). A growing body of evidence suggest that the STIM-dependent calcium signaling is required for mediating cell growth and proliferation of cells of the cardiovascular system.

We used the Cre-lox technology approach to generate smooth muscle cells (SMC) and cardiac specific STIM knock-out SM-STIM1-, sm-STIM2-, and sm-TIM1/STIM2-KO mice, this model allowed us to systematically analyze the physiological role of STIM in smooth muscle cells and the heart.

SM-STIM1-KO mice showed a reduced body weight when compared to control mice. Smooth muscle containing organs, such as intestine and aorta harvested from SM-STIM1-KO mice revealed morphological abnormalities when compared with organs harvested from control mice. Vascular reactivity analyzed using wire myography revealed that while depolarization-induced aortic contraction was unchanged, phenylephrine-mediated contraction was reduced by 26%, and store-dependent contraction was almost eliminated in aortas isolated from SM-STIM1-KO mice. Neointima formation induced by partial carotid artery ligation was suppressed by 54%. Consistently, *in vitro* PDGF-induced SMC proliferation was also reduced by 79% in STIM1-KO SMC. Defective Ca2+ homeostasis in STIM1 KO smooth muscle cells prevents PDGF-induced NFAT activation in both contractile and proliferating SMCs. In conclusion, our data show that STIM1-regulated Ca2+ homeostasis is required for NFAT-mediated transcriptional control, SMC proliferation, development, and growth during physiological as well as pathophysiological conditions.

Biography

Salvatore Mancarella, Ph.D. is an Assistant Professor at the University of Tennessee Health Science Center. As a graduate student and postdoc he has devoted his career investigating how calcium fluctuations control cardiac contraction. Recently Dr. Mancarella is focusing on understanding how calcium signaling at the sub-membrane space is deciphered into the nucleus to control cell growth and proliferation.