Second International Calcium Channel Conference - Placencia, Belize
March 28 – April 2, 2010

Regulation of calcium channels by the ERAD complex

Christophe Altier, Agustin Garcia-Caballero, Brett Simms and Gerald W. Zamponi

Department of Physiology and Pharmacology, University of Calgary, Calgary, Canada

The plasma membrane expression levels of voltage gated calcium channels are important means for regulating the calcium homeostasis of excitable cells, and downstream cell signalling events. The auxiliary Cavβ subunit is such a regulator of calcium channel density in the plasma membrane, but the precise mechanisms by which this is accomplished are not known. We present evidence that the Cavβ subunit increases membrane expression of Cav1.2 channels by antagonizing the entry of the channels into the proteasome. In the absence of Cavβ, Cav1.2 channels become subject to ubiquitination by a ubiquitin ligase and then interact with the ERAD proteins Derlin-1 and p97. This in turn targets the channels to the proteasome for degradation. The proteasomal inhibitor MG132 rescues Cavβ-free channels from degradation and results in their trafficking to the plasma membrane. The coexpression of Cavβ blocks the initial ubiquitination step, thus facilitating the export of the channels from the ER. Our data therefore identify a novel role of the Cavβ subunit in regulating the stability of the calcium channel complex.