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Store-Operated Calcium Entry, STIM proteins and their new partners in neurons

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Abstract

Control of intracellular Ca^{2+} is essential for the functioning of all cell types. Depletion of Ca^{2+} in endoplasmic reticulum (ER) activates a process called Store-Operated Calcium Entry (SOCE). The process relies on refilling the ER with Ca^{2+} ions following their previous release to the cytoplasm. The cooperation of ER calcium sensors STIM1 and STIM2 with the calcium channel ORAI1 is crucial for the functioning of SOCE in non-excitable cells. Emptying the ER Ca^{2+} stores causes STIM proteins oligomerization and translocation of the oligomers towards the plasma membrane, where they form complexes known as "puncta" with ORAI1 calcium channel in plasma membrane.

Our research led to the identification and characterization of STIMs in the brain and neurons (1, 2). Both STIMs are involved in Ca^{2+} homeostasis in neurons (1) and form complexes with endogenous ORAI1 (4), but play distinct roles in SOCE (3). We showed that in neurons STIM1 is a major player in activating SOCE to restore calcium level in ER, while STIM2 regulates the resting calcium level in ER and Ca^{2+} leakage (3, 4). In contrast to non-excitable cells, Ca^{2+} influx in neurons is modulated mainly by voltage-gated Ca^{2+} channels and ionotropic receptor-operated Ca^{2+} channels. We found a physical association of endogenous STIM proteins with endogenous GluA1 or GluA2 subunits of AMPA receptors (AMPAR). To assess the role of AMPAR in SOCE, they were inactivated in cortical neurons by their specific inhibitors, which decreased thapsigargin-induced Ca^{2+} influx. These data suggest an involvement of AMPAR in SOCE and its link with STIM proteins (5). To confirm these observations electrophysiological approaches have been initiated in collaboration with Filip Maciąg.

These data unravel the role of STIM proteins in the influx of Ca^{2+} *via* ORAI channels as well possibility that other entry routes exit in addition to ORAI and Transient Receptor Potential Cation Channels. The discovery of the new proteins interacting with STIM proteins will allow a better understanding of the mechanisms of SOCE. In conclusion, our results describe a new role for STIM proteins in neuronal signaling.

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1. Klejman* M., **Gruszczynska-Biegala*** J., Skibinska-Kijek A., Wisniewska M.B., Misztal K., Blazejczyk M., Bojarski L., Kuznicki J. (2009) Expression of STIM1 in brain and puncta-like colocalization of STIM1 and ORAI1 upon depletion of Ca^{2+} store in neurons. ***Neurochem Int***. 54:49-55. * first co-authors

2. Skibinska-Kijek A., Wisniewska M.B., **Gruszczynska-Biegala J**., Methner A., Kuznicki J. (2009) Immunolocalization of STIM1 in the mouse brain. ***Acta Neurobiol. Exp***. 69:413-28.

3. **Gruszczynska-Biegala J**, Pomorski P, Wisniewska MB, Kuznicki J. (2011) Differential Roles for STIM1 and STIM2 in Store-Operated Calcium Entry in Rat Neurons. ***PLoS ONE*** 6:e19285.

4. **Gruszczynska-Biegala J**., Kuznicki J. (2013) Native STIM2 and ORAI1 proteins form a calcium-sensitive and thapsigargin-insensitive complex in cortical neurons. ***J Neurochem.*** 126(6):727-38.

5. **Gruszczynska-Biegala J**., Sladowska M., Kuznicki J. (2016) AMPA Receptors Are Involved in Store-Operated Calcium Entry and Interact with STIM Proteins in Rat Primary Cortical Neurons. ***Front Cell Neurosci***. Oct 25;10:251.