STIM proteins as regulators of neuronal store-operated calcium influx

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The store-operated calcium channels (SOC) were initially described in nonexcitable cells, such as T cells in the immune system [1]. In neurons, the presence of SOC has been controversial [2]. The main argument against neuronal SOC (nSOC) is that neurons possess many other calcium-permeable channels with high conductance, such as NMDA receptors and voltage-gated calcium channels. The existence, functional relevance and molecular identity of nSOC are still under investigation. However, recent molecular analysis of nSOC provided support to its existence and importance for neuronal function.

SOC is mediated by two main components: endoplasmic reticulum (ER) Ca^{2+} sensors STIM1 or STIM2 proteins [3] and plasma membrane (PM) Ca^{2+} channels from Orai and TRPC protein families [1]. SOC in nonexcitable cells is activated by ER Ca^{2+} depletion in response to activation of inositol (1,4,5)-trisphosphate receptors and Ca^{2+} release from the ER. ER Ca^{2+} concentration is sensed by helix-loop-helix structural domain (EF hand domain) in the luminal portion of STIM1. Following Ca^{2+} depletion from the ER, STIM1 forms oligomers and translocates to ER–PM junctions [1]. Once located to ER–PM junctions, STIM1 binds to Orai proteins and activate SOC Ca^{2+} influx, leading to an increase in intracellular Ca^{2+} concentration. This cytoplasmic Ca^{2+} abundance is sequestered by SERCA pump to the ER, refilling the stores. The EF hand domain of STIM2 proteins has significantly lower affinity for Ca^{2+} than STIM1, and it has been established that STIM2 proteins primarily control steady-state ER and cytosolic Ca^{2+} homeostasis [4].

Both STIM1 and STIM2 proteins are expressed in hippocampal neurons [5], and both of these proteins have been implicated in control of nSOC. Klejman *et al.* observed that STIM1 is colocalized with Orai1 upon depletion of Ca^{2+} stores in dendrites and soma [6]. More recent reports suggested that STIM1 and Orai1 are colocalized and may interact with synaptopodin, a protein that regulates synaptic plasticity in hippocampal dendritic spines [7]. Activation of STIM1 and nSOC was described in hippocampal neurons following activation of type I metabotropic glutamate receptors (mGluR) or muscarinic acetylcholine receptors (mAChR) [8]. Notably, nSOC-independent functions of STIM1 in hippocampal neurons were also reported. It was suggested that STIM1 directly controls level of phosphorylation and surface expression of the AMPAR [9]. The role of STIM1 in control of neuronal L-type Ca^{2+} channel activity [10] and feedback regulation of Ca^{2+} signals in presynaptic terminals was reported [11]. Using optically controlled construct OptoSTIM1, Kyung *et al.* demonstrated that expression and activation of this construct in mouse hippocampus is able to induce nSOC Ca^{2+} influx and promote contextual memory formation [12]. Majewski *et al.* observed improvements of contextual learning in STIM1 overexpressing mice [13]. These authors further demonstrated that overexpression of STIM1 does not influence long-term potentiation (LTP) induction in acute hippocampal slices, however, blocks DHPG-dependent long-term depression (LTD) [13]. The mice with forebrain-specific knockout of STIM1 and STIM2 were analyzed by Garcia-Alvarez *et al.* [14]. These authors reported a mild learning delay in *Stim1* cKO mice, while learning and memory in *Stim2* cKO mice was

normal. However, deletion of both *Stim* genes resulted in a pronounced impairment in spatial learning and memory and in enhanced LTP [14].

STIM2 is a predominant isoform in the hippocampus [5,15]. Genetic deletion of STIM2 protein impaired SOC and confers protection from neurological damage in a model of focal cerebral ischemia [16]. A recent study by Korkotian *et al.* suggested that STIM2 moves to dendritic spines and regulates Orail-mediated nSOC [17]. It has been reported that STIM2, but not STIM1, influences the formation of excitatory dendritic spines and shapes basal synaptic transmission in excitatory neurons [9,18]. These authors concluded that STIM2 functions in an nSOC-independent manner by regulating phosphorylation and surface expression of the AMPAR [9]. The same group reported that STIM2 is required for the stable expression of both LTP and LTD at CA3–CA1 hippocampal synapses [18]. Our laboratory reported that virus-mediated knockdown of STIM2 protein expression causes mushroom spine shrinkage and causes loss of nSOC in hippocampal dendritic spines [19]. Moreover, it has been observed that STIM2 hyperexpression as well as pharmacological activation of nSOC in the hippocampus is able to protect mushroom spines in different models of Alzheimer's disease (AD) pathology [15,19–20]. Downregulation of STIM2 proteins was observed in cells from AD patients and in AD mouse models [19,21]. Based on these results we suggested that nSOC-mediated Ca^{2+} influx is needed to maintain continuous activity of CaMKII in the spines, supporting stability of mushroom spines [19,22].

As it is clear from this brief summary, we are still trying to understand the roles of STIM1 and STIM2 proteins in neurons. Some groups suggest that in neurons STIM1 and STIM2 proteins function in SOC-independent manner [9–11]. Other groups concluded that similar to nonexcitable cells, STIM1 and STIM2 proteins mediate nSOC. It is possible that STIM1 and STIM2 play both nSOC-related and unrelated roles in neurons. Observed discrepancies are likely to be caused by differences in experimental models and protocols. Nevertheless, learning and synaptic plasticity phenotypes observed in STIM1 and STIM2 knockout and overexpression models [12–14,16] suggest that these proteins clearly play a role in neuronal function. It is likely that the main role of nSOC in neurons is signaling and not just refilling of the stores [23]. Future studies will further clarify roles of STIM1 and STIM2 proteins in neuronal physiology.

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