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AUTOCOMMENTARY

Orai1 regulates calcium entry into dendritic spines

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The possible role of store operated calcium entry (SOCE) through the Orai1 channel in central neurons has attracted growing attention in recent years because of its involvement in regulation of calcium homeostasis in the neuron. One unique neuronal compartment associated with calcium homeostasis is the dendritic spine, the site of excitatory synapses in the majority of neurons in the brain. It has been linked to neuronal plasticity, which is highly regulated by calcium influx during intense synaptic activity. The formation, plasticity and longevity of dendritic spines have been studied extensively, but the rules governing these processes are still not clear and not universal. The cultured hippocampal neuron provides a convenient vehicle to study the role of SOCE channels in dendritic spine formation and plasticity. Indeed, recent studies have detected the presence of Orai1 channels in central neurons,[1,2] and further studies indicated that STIM2, the sensor for endoplasmic reticulum calcium store depletion, is instrumental in maintenance of mature dendritic spines in cultured hippocampal neurons.[3,4] We have recently analyzed the role of Orai1 in dendritic spine formation and plasticity. This study follows our interest in the role of calcium stores in spine plasticity, where we found that dendritic spines contain ryanodine receptor-type calcium stores.[5] In the more recent study,[6] we employed plasmids that encode the Orai1 protein, as well as plasmids that encode the dominant negative (DN) Orai1. We also knocked down Orai1, using selective siRNA for this protein. In calcium store-depleted neurons a transient elevation of extracellular calcium concentration ($[Ca^{2+}]o$) caused a rise in $[Ca^{2+}]i$ that was mediated by activation of the SOCE. The store depletion resulted in an increase in STIM2 association with Orai1 in dendritic spines. The response to the rise in $[Ca^{2+}]o$ was larger in spines endowed with a cluster of Orai1 molecules than in spines devoid of Orai1. Furthermore, topical application of calcium-containing medium, in a calcium-free extracellular environment, could trigger the formation of novel dendritic spines, and their location was highly correlated with the presence of Orai1 cluster (Fig. 1). Transfection of neurons with DN-Orai1 resulted in retarded maturation of dendritic spines, a reduction in synaptic connectivity with afferent neurons and a reduction in ability to undergo morphological changes following induction of chemical LTP. Likewise, siRNA-treated neurons had fewer mature dendritic spines, and lower rates of spontaneous mEPSCs compared to scrambled control siRNA-treated neurons. Thus, our results indicate that Orai1 channels are effective in causing a transient rise in $[Ca^{2+}]i$ in dendritic spines so as to facilitate maturation of dendritic spines and functional synapses in central neurons. It is hypothesized that in the absence of active synapses, either because presynaptic fibers still did not yet arrive, or are prevented from releasing neurotransmitters, the presence of Orai1 will serve to load a local rise of $[Ca^{2+}]I$, sufficient for the dendrite to facilitate formation of protrusions, which upon interactions with a presynaptic-terminal, be converted to mature spines. Thus, Orai1 is assumed to be instrumental in formation of spines.[7] It is still unclear which is the "partner molecule" that is linked to Orai1, and it could either be STIM1 (2) or STIM2 (3). Both of them are present in hippocampal neurons, in different

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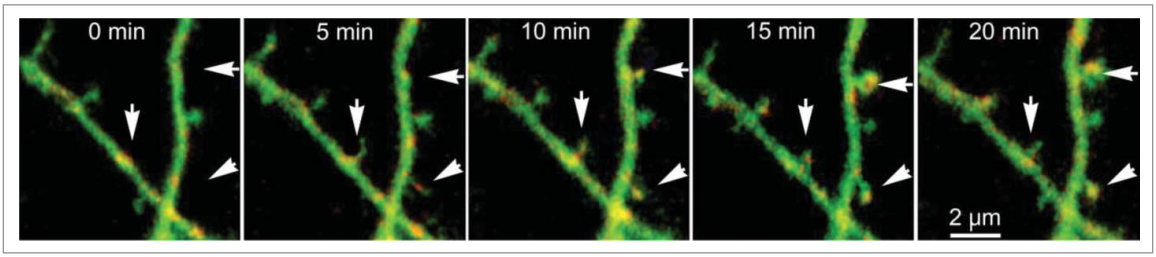

Figure 1. Dendritic segments of a neuron that had been transfected with GFP (green) and Orai1-mCherry (red). The culture was imaged in the nominally calcium-free medium, and exposed to a pulse application of an extracellular medium, containing calcium. The cell was imaged in time-lapse mode over a period of 20 minutes and the formation/deletion/changes in short dendritic protrusions was marked. New dendritic spines were formed over this observation time, and most of them were associated with the presence of a Orai1 puncta (arrowheads). In fact, the location of nascent spines could be predicted based on the presence of Orai1 punctum inside the dendritic spine (left, arrows). (Modified from ref [6]).

concentrations and distribution.[6] The demonstration that STIM2 is important for spine maintenance, and that it is linked to presenilin, a pivotal molecule in the neurodegenerative Alzheimer disease,[3,4] re-assigns a key role for calcium homeostatic mechanisms in the development of AD. Further studies should clarify the relations among the different components of the SOCE channels, and their relevance to calcium stores and neurodegenerative diseases.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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