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(REVIEW ARTICLE)

Functions and regulations of the Store Operated CRAC channels

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Abstract

Store-operated Ca^{2+} channels, or SOCs, contain the main Ca^{2+} activated-receptor signaling pathways in non-excitable cells and play key roles in several biological and signaling pathways such gene, Ca^{2+} secretion and homeostasis and the differentiation of cells. Ca^{2+} signaling is associated with CRAC channels and it is essential and critical for activation of T and B cells. Cell receptors stimulated by antigens thus lead to the accumulation of huge and distinct CRAC signaling complexes. Several studies have revealed in mast and T cells Ca^{2+} influxes across plasma membrane and SOC activation after depletion of intracellular Ca^{2+} pool. Targeting CRAC channels pharmacologically have the possible therapy to be used therapeutically for angiogenesis modulation in many tumors, metabolic disorders such as fatty liver diseases, obesity or for autoinflammatory diseases and allergic conditions.

Keywords: CRAC channels; Ca^{2+}; STIM; Orai; RNA interference

1. Introduction

Ca^{2+} signaling has an important role in different biological processes such as embryonic development, transcription of genes, muscle action excitable cells action and permeability of some ion channels. The ability of Ca^{2+} signaling relay on the concentration's differences between cytosolic concentration and ER concentration. Moreover, Ca^{2+} channels opening has a pivotal role in this signaling. Normally, Ca^{2+} releases from the ER after activation by IP3. In this review, we will try to illustrate one remarkable rout for controlling Ca^{2+} concentration, which is the calcium release-activated calcium (CRAC) channels. Our focus here will be on the identification, the main molecular components, functions, activation, and regulation of the CRAC channels.

2. Calcium Release-Activated calcium (CRAC) Channels

CRAC channels are store-operated channels (SOC) in the plasma membrane. SOC are the main and important mechanism used to elevate Ca^{2+} concentration in excitable and non- excitable cells. Over the last two decades, most of the researchers have showed in mast and T cells Ca^{2+} influxes across plasma membrane and SOC activation after depletion of intracellular Ca^{2+} pools (1). Previous researchers clarified that Ca^{2+} current activated by different stimuli that lowered Ca^{2+} store and this current was the same, which they had formerly described. At this time the authors named these channels as CRAC and the current as (*I*CRAC) (2).

Ca^{2+} signaling is associated with CRAC channels that is essential and critical for activation of T and B cells. Cell receptors stimulate by antigens thus lead to the accumulation of huge and distinct CRAC signaling complexes. In T and B cells increasing the Ca^{2+} concentration is mediated by CRAC channels activation which is modulated by a regulatory membrane protein (3).

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Additionally, lacking any of the essential components in CRAC channels causes multiple defects in translocation of nuclear activated T cells and cytokines expression. Ca^{2+} is necessary for activation T and B cells gene expression. Furthermore, several studies showed that there are many human immunodeficiencies, which are characterized by falling in the total numbers of inflammatory cells and immunoglobulin. Moreover, mutation in CRAC channels completely diminished the activation and proliferation of T cells (4).

3. The components of CRAC channels

The essential components of CRAC channels are stromal interaction molecules (STIM) and Orai. STIM was identified first then Orai was discovered. Many approaches were used to identify these components, human STIM1 and STIM2 were identified by using RNA interference (RNAi) –based screen in HeLa cells. The principle of this approach depends on finding the genes that are responsible for changing Ca^{2+} entry. At the same time, STIM in *Drosophila* cell identified by the same approach. Also, they demonstrated that STIM is the Ca^{2+} sensor and that its activation occurs after Ca^{2+} depletion (5,6). Orai was discovered by RNA unbiased genome wide screen using platform for genome –wide screen in *Drosophila*, and there are three types of Orai and each one has a distinct property (7,8). Additionally, use of immunofluorescence with polyclonal antibodies determined the distribution of overexpressed STIM1 proteins (9). Biophysical fingerprinting was used to clarify the biophysical and pharmacological properties of CRAC, such as, ion selectivity, pore diameter, activation, inactivation of Ca^{2+} current, and the influence of domains and drugs in CRAC channels actions (4).

The depletion of ER-Ca stores activates store operated Ca^{2+} entry (SOCE). SOCE is a critical process for immune cells activity and for a variety of excitable and non-excitable tissues. The researchers then studied the property of each compartment, STIM was identified as an ER Ca^{2+} sensor because of the ability of negatively charged residues in the EF hand to sense luminal Ca^{2+} concentration. In addition, STIM has two essential functions: it acts a sensor for ER Ca^{2+} depletion, and functions to oligomerize and cluster Ovai (10). The genetic evidence revealed that Oria form a pore in CRAC channel constitutes and the permeation pathway for Ca^{2+}, formed by highly negative side chain charges of the trans, membrane domain. Moreover, there are much mutagenic evidence to confirm that high Ca^{2+} selectivity can be reduced by replacement of these residues. Two other types of Orai family are present in any cell but mutagenic defect of Orai1 gene cannot be compensated by normal genes of Orai2 and Orai3 (11).

These properties of CRAC components give a rise to the study of the mechanism of regulation of CRAC channels. In the resting state, STIM travels through ER associated with EB1 (microtubule tracking protein). When ER-Ca^{2+} depletion occurs, STIM dissociates from EB1 and aggregates into a complex at the ER plasma membrane and forms the clusters. The activation of the CRAC channels and Ca^{2+} influx of accomplished by additional binding of STIM to the N-termini of Orai. This process led to refilling of the intracellular Ca^{2+} store. Regeneration of Ca^{2+} stimulates STIM/ Orai complex dissociation and stops the process. (10).

STIM has two pathways to transmit the signal for Orai activation, either by simple interaction or via further modulatory proteins that have a role in regulation and activation of STIM/Orai complex (10). Recently, new proteins have been discovered that have a modulatory role in STIM oligomerization and clustering. They protect the cell from higher Ca^{2+} concentration by regulation of SOCE activity, or they have an alternative pathway to recruit STIM on to the plasma membrane rather through binding of Ca^{2+} (12).

Important results came from a new study, which revealed that the activation and inactivation of CRAC channels follow nonlinear STIM/Orai ratio functions, the 2:1 ratio is sufficient to trap CRAC channels (13). Furthermore, there are other pathways to activate the CRAC channels. For instance, STIM is activated via changes in temperature leading to enhanced STIM movement and clustering (14). Recent study revealed a new element that has a novel role in the regulation and increase the activity of CRAC components STIM/Orai called serum and glucocorticoid-inducible kinase (SGK1), which regulates transcription factor nuclear factor (NF-*k*B). Moreover, it enhances the expression of Orai and activates STIM which control Ca^{2+} entry and promote cellular movement (15).

4. Functions of CRAC channels

There are many functions of CRAC channels beside their role in immune cells. Some studies found that STIM is necessary and sufficient to promote cardiac hypertrophy (16). Another study showed that inhibition of Ca^{2+} entry through SOCS and STIM may be responsible for enhancing the cholestatic bile acid condition, deficiency of Orai and Store Ca^{2+} entry causes myopathy and ectodermal dysplasia. Additionally, a lack of STIM or Orai in mice leads to defect in thrombus formation (17,18). A new type of STIM protein named STIML allows immediate activation of SOCE through interaction

with Orai Ca^{2+} channel thus forming stable cluster via interaction with actin (19). Furthermore, a recent study showed that STIM/Orai proteins are involved in controlling the development of different cancers such as, breast and cervix cancers. Likewise, STIM/Orai proteins are essential for increased cells proliferation, escape from apoptosis, and cell invasion (20).

5. Conclusion

There are many things we could propose to demonstrate the novel role of CRAC channels. For instance, using of 3D atomic resolution to identify the direct interaction between STIM and Orai, mutagenic approaches to study the components and the properties of Orai2 and Orai2 proteins, employment the NMR to differentiate some specific amino acid that form domains in both proteins and using the sophisticated devices to monitor the biophysiological properties of CRAC channels.

Pharmacological targeting of CRAC channels have the potential to be used therapeutically for angiogenesis modulation in many cancers, metabolic disorders such as obesity or for diseases such as autoinflammatory diseases and allergy.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflicts of interest.

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