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Ca^{2+} influx at the ER/PM junctions

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ABSTRACT

Ca^{2+} influx across the plasma membrane is a key component of the receptor-evoked Ca^{2+} signaling that mediate numerous cell functions and reload the ER after partial or full ER Ca^{2+} store depletion. Ca^{2+} influx is activated in response to Ca^{2+} release from the ER, a concept developed by Jim Putney, and the channels mediating the influx are thus called store-operated Ca^{2+} influx channels, or SOCs. The molecular identity of the SOCs has been determined with the identification of the TRPC channels, STIM1 and the Orai channels. These channels are targeted to, operate and are regulated when at the ER/PM junctions. ER/PM junctions are a form of membrane contact sites (MCSs) that are present in all parts of the cells, where the ER makes contacts with cellular membranes and organelles. MCSs have many cellular functions, and are the sites of lipid and Ca^{2+} transport and delivery between organelles. This short review discusses aspects of MCSs in the context of Ca^{2+} transport.

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1. Introduction

Membrane contact sites (MCSs) are present in many cellular compartments. The endoplasmic reticulum (ER) forms most MCSs by tethering with the plasma membrane (PM), mitochondria, endosomes, lysosomes, peroxisomes, and in yeast with the vacuole [1–5]. Most information on the structure and function of MCSs came from studies of lipid synthesis and transfer in yeast, although similar information in mammalian cells is rapidly accumulating, as new tools for their studies become available (for recent reviews see [2,4,6]). MCSs have many functions in cell metabolism and signaling. MCSs is where lipid synthesis complexes and lipid transport proteins are located and where lipid synthesis and transport between organelles take place [5,6]. Many signaling proteins resides at MCSs or are recruited to MCSs during cell stimulation [2,4,6], as is the case with Orai1 and STIM1 [7–10]. Mitochondrial fission takes place at MCSs, as well as initiation of autophagy and mitophagy [2,6]. In the case of Ca^{2+} signaling, the ER/PM junctions are the MCSs at which the STIM1-Orai1 and STIM1-TRPC channels complexes assemble to mediate the store-operated Ca^{2+} influx (SOCs) [10–12]. Ca^{2+} transfer between the ER and mitochondria takes place at the ER/mitochondria MCSs [13,14].

2. The ER/PM MCSs

Examining lipid transfer between the ER and plasma membrane (PM) in yeasts identified several of the tether proteins at the ER/PM junctions. They include the three Tricalbins, the Increased sodium tolerance protein 2 (Ist2) and the ER resident Scs2/22 [1,15]. Deletion of all six proteins was necessary to dissociate the ER/PM junctions in yeast [15]. The mammalian homologues of these proteins are known to a limited extent. The Tricalbins homologues are the three extended synaptotagmins (E-Syts) [16,17], and the Scs2/22 homologues are VAP-A and VAP-B [4]. The yeast Tricalbins and the mammalian E-Syts have a synaptotagmin-like mitochondrial and lipid binding protein (SMP) domain [18,19]. The SMP domain is present in many tether proteins, in various cellular compartments and was shown recently to mediate lipid transfer between bilayers [20,21]. The homologue of Ist2 is not known yet, although Ist2 shows homology to the Anoctamins, a family of 10 proteins with diverse functions, including Ca^{2+}-activated Cl^- channels (ANO1 and ANO2) [22] and lipid scrambling (ANO6 and others) [23–25]. Whether Ist2 mediates lipid transfer, exchange or scrambling is not known.

Other proteins that may reside at the same or adjacent to the ER/PM junctions are the oxysterol-binding protein-related proteins (ORPs) ORP5 and ORP8 [26–28] and the lipid transfer proteins Nir2 and Nir3 [29,30]. ORP5/8 mediate PS/PI4P exchange to deliver PS to the plasma membrane and PI4P to the ER [26–28]. Nir2 clusters at the ER/PM junction in response to cell stimulation and replenishes PM $PI(4,5)P_2$ and $PI(3,4,5)P_3$ [4,29,30]. An important function

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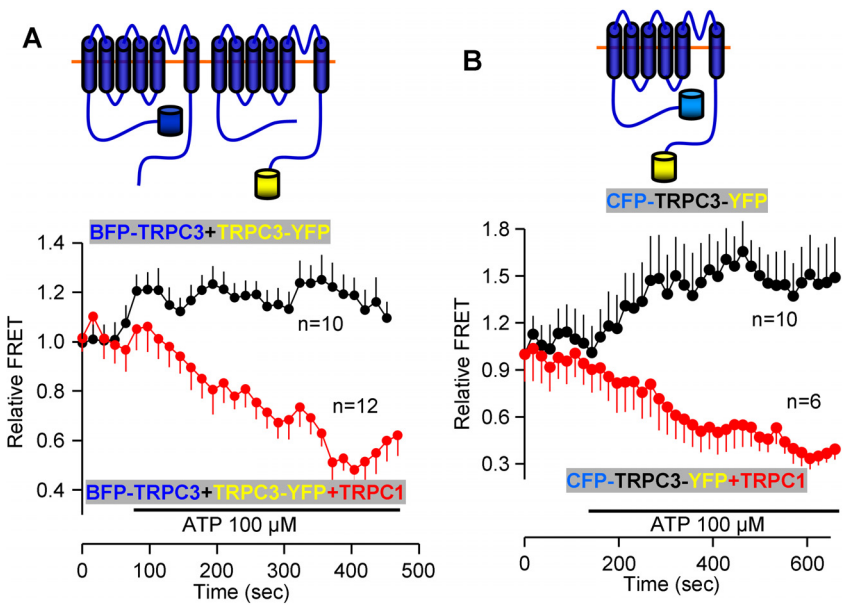

Fig. 1. TRPC1 dissociates TRPC3 N and C terminal coiled-coil domains.
(A) BFP-TRPC3 and TRPC3-YFP were co-expressed alone of together with TRPC1 in HEK cells. Cell stimulation slightly increased TRPC3-TRPC3 interaction in the absence of TRPC1 (black symbols and trace), while TRPC1 caused dissociation of interacting TRPC3 monomers (red symbols and trace). (B) similar experiment as in (A) except that TRPC3 was double tagged with BFP at the N terminus and YFP at the C terminus. In this case, TRPC1 dissociates the interaction between the same molecule TRPC3 N and C termini coiled-coil domains.

of Nir2 reported recently is transfers PI from the ER to the PM and at the same time transfer PA from the PM to the ER, suggesting that Nir2 functions as PI/PA exchanger [31]. The topics of lipid transfer and the structure and function of the ER/PM junctions are relatively new, at least in mammalian cells, and new components are continually being identified.

3. Ca^{2+} signals at MCSs

The best documented Ca^{2+} signaling at MCSs are Ca^{2+} signaling at the ER/mitochondria and Ca^{2+} influx by store operated Ca^{2+} channels (SOCs). Ca^{2+} signaling at the ER/mitochondria are discussed at length elsewhere [13,32] and we have restricted our short comments to the function of the SOCs. The concept of SOCs was introduced to explain fluid and electrolyte secretion by secretory glands [33]. In the revised version of the hypothesis it was postulated that Ca^{2+} release from the ER in response to cell stimulation somehow results in activation of Ca^{2+} influx pathway at the plasma membrane [34]. At about the same time, we showed that Ca^{2+} influx across the plasma membrane in response to store depletion to reload the ER with Ca^{2+} takes place at free cytoplasmic Ca^{2+} concentration close to the resting levels [35,36]. This is due to the high capacity of Ca^{2+} uptake by the sarco/endoplasmic reticulum (SR) calcium transport ATPase (SERCA) pump compared to the rate of Ca^{2+} influx by the SOCs [36]. The concept of SOCs then received decisive evidence with the demonstration that passive store depletion by inhibition of the SERCA pump with thapsigargin activated the same Ca^{2+} influx pathway as the receptor-stimulated depletion of ER Ca^{2+} [37]. The next step was recording the Ca^{2+}-release activated current (CRAC) [38] and identification of the TRPC channels as receptor activated Ca^{2+} influx channels [39,40], although the TRPCs did not mediate the CRAC current. The finding of STIM1 [9,41] and Orai1 [42–44] and that STIM1-Orai1 complexes mediate the CRAC current [43,45] established the molecular components of the SOCs. Clustering of STIM1, Orai1 and the TRPC channels at ER/PM junctions [11,46] highlighted the importance of the ER/PM junction in SOCs channels function.

TRPC channels can function in both store-dependent and store-independent modes [47,48]. When they function in a store-dependent mode, they are regulated by STIM1 [48–50], and are strictly dependent on the STIM1 polybasic, $PI(4,5)P_2$ interacting domain and two conserved negative charges in the C terminus of the TRPC channels [49,50]. Moreover, gating by STIM1 of several TRPC channels requires their interaction [47,48]. An example is shown in Fig. 1 in which TRPC1 interacts with TRPC3 to dissociate the interaction between the two TRPC3 coiled-coil domains [47], which is required for regulation of TRPC3 by STIM1 [49,50]. For TRPC channels to be regulated by STIM1, they must be present at the ER/PM junctions where STIM1 clusters are found. Indeed, extensive studies showed the recruitment of TRPC1 to the STIM1 puncta [11] a process facilitated by STIM2 [51]. In native cells STIM1, Orai1 TRPC1 [52] and TRPC3 [53] are found at the sites at which STIM1 is recruited by store depletion to form complexes that can be immunoprecipitated after ER Ca^{2+} store depletion [52].

The properties and mechanism of activation of Orai1 by STIM1 is discussed elsewhere in this special issue. For the current discussion, it should be noted that STIM1 fulfills all the properties of a tether protein. STIM1 has N-terminal transmembrane domain that spans the ER membrane, a long cytoplasmic domain that bridges the distance between the ER and PM and a C terminal polybasic domain that binds $PI(4,5)P_2$ at the PM. At the junctions, STIM1 clusters both Orai1 and the TRPC channels. The ER/PM junctions at which STIM1 clusters are formed by tether proteins. Establish tethered are E-Syt1 [10,17] and Nir2/3 [4,30,31]. Another likely tether is a mammalian homologue of Ist2 that can be one of the ANO proteins.

Localization of the STIM1-Orai1 complex at the ER/PM junctions defines the Ca^{2+} entry sites at the plasma membrane. Moreover, the STIM1-Orai1 complex activity is specifically regulated by Ca^{2+} only when it is at the ER/PM junctions and is experiencing high levels of $PI(4,5)P_2$ [10]. This is illustrated in Fig. 2. Ca^{2+} influx by Orai1 is inhibited by high Ca^{2+} in two modes, fast Ca^{2+}-dependent inhibition that is completed in 100 msec and slow Ca^{2+}-dependent inhibition (SCDI) that is completed in 1–2 min [54]. Both forms of inhibition are mediated by the ER resident protein SARAF [10,55]. Ca^{2+}-dependent inhibition (CDI) requires stabilization of the ER/PM