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The closing and opening of TRPC channels by Homer1 and STIM1

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Abstract

Ca^{2+} influx is a central component of the receptor-evoked Ca^{2+} signal. A ubiquitous form of Ca^{2+} influx comes from Ca^{2+} channels that are activated in response to depletion of the endoplasmic reticulum Ca^{2+} stores and are thus named the store-operated Ca^{2+}-influx channels (SOCs). One form of SOCs is the Transient Receptor Potential Canonical (TRPC) channels. A major question in the field of Ca^{2+} signaling is the molecular mechanism that regulates the opening and closing of these channels. All TRPC channels have a Homer binding ligand and two conserved negative charges that interact with two terminal lysines of the Stromal Interacting Molecule 1 (STIM1). The Homer and STIM1 sites are separated by only four amino acid residues. Based on available results, we propose a molecular mechanism by which Homer couples TRPC channels to IP_3 receptors (IP_3Rs) to keep these channels in the closed state. Dissociation of the TRPCs-Homer-IP_3Rs complex allows STIM1 access to the TRPC channels negative charges to gate open these channels.

Introduction

The receptor-evoked Ca^{2+} signal begins with the activation of phospholipase C (PLCβ or PLCγ) to generate inositol trisphosphate (IP_3), which releases Ca2+ from intracellular stores, primarily the endoplasmic reticular stores (Berridge and Irvine, 1989). The IP_3-mediated Ca2+ release launches the Ca^{2+} signal that involves cyclical activation of Ca^{2+} channels and Ca^{2+} pumps to generate multitude of Ca^{2+} signals in the form of Ca^{2+} puffs, blinks and sparks that can coalesce into cyclical Ca^{2+} increases to generate Ca^{2+} oscillations and/or to propagate Ca^{2+} in the form of waves (Berridge, 2006). These Ca^{2+} signals control a plethora of physiological functions essential for cell survival, specialized cell functions, and eventually cell death (Berridge et al., 2003). A crucial component of all receptor-evoked Ca^{2+} signals is Ca^{2+} influx across the plasma membrane. Ca^{2+} influx is activated in response to Ca^{2+} release from internal stores, most commonly the endoplasmic reticulum (ER) (Parekh and Putney, 2005). Ca^{2+} influx is essential to maintain the physiological Ca^{2+} oscillations and to provide the Ca^{2+} for replenishment of the Ca^{2+} store at the end of the stimulated period (Kiselyov et al., 2006). Ca^{2+} influx also directly mediates many cellular functions on time scales from msec, such as exocytosis (Pang and Sudhof, 2010), to days, such as gene regulation (Di Capite et al., 2009) and cell death (Supnet and Bezprozvanny, 2010).

The receptor-evoked store-operated Ca^{2+} influx is mediated by two types of Ca^{2+} influx channels: the Orai family (Hogan et al., 2010) and TRPC family channels (Lee et al., 2010a; Worley et al., 2007b), and are gated by the endoplasmic reticulum (ER) Ca^{2+} sensor STIM1 (Liou et al., 2005; Roos et al., 2005). The TRPC channels are also gated by the scaffolding

protein Homer1 (Kim et al., 2006; Worley et al., 2007a; Yuan et al., 2003). This short review highlights the potential role of Homer1 and STIM1 in the closing and opening of the TRPC channels.

The Homers

The Homers are a family of three scaffolding proteins: Homer1, Homer2 and Homer3, with numerous isoforms that were discovered in the brain as immediate early genes (Soloviev et al., 2000; Xiao et al., 2000). The Homer1a isoform is rapidly upregulated in response to synaptic activity induced by seizure, or during induction of long-term potentiation. Homer1a is also selectively induced in cells of the hippocampus when rodents engage in exploratory behavior (Brakeman et al., 1997; Kato et al., 1998). All Homers have an Ena VASP Homology 1 (EVH1) domain. Homer1a has a short C-terminal extension, while long-form Homers have a C-terminal coiled-coil domain and two leucine zippers (Tadokoro et al., 1999; Xiao et al., 1998) and Fig. 1A). The N-terminal EVH1 domain of the different Homers are about 60–70% conserved, while the coiled-coil domains show only about 20% sequence identity. The coiled-coils serve to assemble the Homers into elongated tetramers (Hayashi et al., 2006). The tetrameric Homer is likely required to form a lattice with other scaffolds that bind Ca^{2+} signaling proteins in cellular microdomains (Kim and Sheng, 2004; Sala et al., 2005; Tadokoro et al., 1999; Tu et al., 1999; Xiao et al., 2000). The Homers EVH1 domain interacts with and regulates the activity of several Ca^{2+} signaling proteins listed in Fig. 1B that reside in Ca^{2+} signaling complexes. The monomeric Homer1a then disrupts signaling complexes and functions by acting as a negative regulator of the long Homers (Roche et al., 1999; Xiao et al., 1998).

Localization of the Homers and interaction with Ca^{2+} signaling proteins

In neurons, the Homers are found in the Post-Synaptic-Density (PSD) and dendrites, where they interact with the metabotropic glutamate receptors mGluR1 and mGluR5 (Brakeman et al., 1997; Kato et al., 1998; Roche et al., 1999; Tu et al., 1999). Mutation and structural analysis revealed that the EVH1 domain binds to the ligands PPXXF (Barzik et al., 2001; Irie et al., 2002), øPPXF and the LPSSP (Yuan et al., 2003). These ligands are found in the mGluRs and many Ca^{2+} signaling proteins, including Shank (Tu et al., 1999), PLCβ (Hwang et al., 2005; Nakamura et al., 2004), IP_3Rs (Kim et al., 2006; Yuan et al., 2003), TRPC channels (Kim et al., 2006; Yuan et al., 2003), ryanodine receptors (Feng et al., 2002; Hwang et al., 2003; Ward et al., 2004; Westhoff et al., 2003), several L-type Ca^{2+} channel isoforms (Huang et al., 2007; Olson et al., 2005; Yamamoto et al., 2005) and nuclear factor of activated T cells (NFAT) (Huang et al., 2008).

To regulate Ca^{2+} signaling, the Homers have to be present in signaling microdomains. The Ca^{2+} signaling centers in the PSD and dendrites are enriched with Homer proteins (Ango et al., 2000; Dietrich et al., 2005; Fagni et al., 2002; Shiraishi et al., 2003). In polarized cells, Ca^{2+} signaling complexes are clustered at the apical pole, a region expressing Homer1 and Homer2 (Shin et al., 2003). This is reproduced in Fig. 1C taken from (Shin et al., 2003), which shows that Homer1 and Homer2 are restricted to the apical pole of pancreatic acinar cells, whereas Homer3 is enriched at the basal pole. Ca^{2+} signaling proteins are also enriched at the apical pole of polarized cells (Kiselyov et al., 2006) and co-localize with Homer1 and Homer2 (Shin et al., 2003). The C-terminal portion of the Homers coiled-coil domain appears to mediate the subcellular localization of the Homers and is required for clustering of Ca^{2+} signaling proteins (Hayashi et al., 2006).

The three Homers have distinct roles in Ca^{2+} signaling. The role of Homer3 in Ca^{2+} signaling is not well understood. The most intriguing recent finding is that Homer2 and Homer3 regulate NFAT (Huang et al., 2008). These Homers compete with the phosphatase

calcineurin for binding to NFAT and, in effect, sequester NFAT in the cytosol to prevent its dephosphorylation and, thus, translocation to the nucleus (Huang et al., 2008). In this manner, the Homers can regulate all of the many roles of NFAT in cell differential and function. Interestingly, phosphorylation of Homer3 by calcium/calmodulin-dependent kinase II (CaMKII) regulates its targeting to the plasma membrane and its interaction with cytosolic proteins (Mizutani et al., 2008). CaMKII also phosphorylates NFAT at the site dephosphorylated by calcineurin (Crabtree and Olson, 2002). This raises the possibility that a CaMKII-Homer-NFAT-calcineurin complex operates to control the function of NFAT.

In addition to binding of NFAT, Homer2 also regulates signaling by G-protein-coupled receptors (GPCRs) through regulation of the GTPase-activating protein (GAP) activity of Regulators of G proteins Signaling (RGS) proteins and of PLCβ (Shin et al., 2003). Deletion of Homer2 in mice reveals that Homer2 is involved in the pathway that underlies response to cocaine and alcohol (Kalivas et al., 2004; Szumlinski et al., 2005; Szumlinski et al., 2003). In G protein signaling in the unstimulated state, $G_{\alpha q}$ is bound with GDP and is associated with $G_{\beta\gamma}$. Receptor stimulation catalyzes the exchange of GDP for GTP on $G_{\alpha q}$ (Freissmuth et al., 1989; Gilman, 1987). Termination of the signal requires hydrolysis of GTP by $G_{\alpha q}$ that is markedly accelerated by RGS proteins (Ishii and Kurachi, 2003; Ross and Wilkie, 2000) and PLCβ (Ross, 2008). Homer2 accelerates the GAP activity of both RGS proteins and PLCβ to attenuate the intensity of the Ca^{2+} signal (Shin et al., 2003).

Homer1 and gating of TRPC channels

Of all the Homers, the function of Homer1 is best documented and understood. Homer1 binds to mGluRs (Beneken et al., 2000) and to the N-terminus of the IP_3Rs (Yuan et al., 2003), linking them to the Shank proteins to form a Ca^{2+} signaling complex that regulates Ca^{2+} release (Fagni et al., 2002; Sala et al., 2005). Homer proteins also affect interaction and communication of several other Ca^{2+} signaling receptors and proteins in the PSD, as reviewed in (Worley et al., 2007a). Of these interactions, the interaction of Homer1 with TRPC channels and regulation of channel activity by Homer1 have been explored extensively.

A role of Homer1 in the regulation of Ca^{2+} influx was revealed by the increased spontaneous Ca^{2+} influx in cells from which Homer1 was deleted (Yuan et al., 2003). TRPC channels express the Homer binding ligand øPPXF in their C-terminus. Accordingly, Homer proteins bind to all TRPC channels and assemble them into complexes with IP_3Rs (Yuan et al., 2003). Disruption of the Homer binding ligand of the TRPC channels prevents their binding to Homer. Most notably, disruption of the TRPC1-Homer-IP_3Rs complex by mutation in the Homer ligand or by expression of Homer1a results in spontaneously active TRPC channels (Yuan et al., 2003). Moreover, cell stimulation results in IP_3-dependent dissociation of the TRPCs-Homer1-IP_3Rs (Kim et al., 2006). These findings clearly indicate that Homer1 is essential to maintain the TRPC channels in the closed state. At the basal state, TRPC channels are present in a complex with IP_3Rs that is formed by the long Homer1b/c to keep the channel inactive. Upon cell stimulation, the complexes are dissociated to allow activation of TRPC channels.

STIM1

STIM1 was discovered by a search for the molecular identity of the Ca^{2+} influx pathway and its regulators. In particular, STIM1 is the molecule that mediates the communication between ER Ca^{2+} load and activation of the Ca^{2+} influx channels at the plasma membrane (Liou et al., 2005; Roos et al., 2005). The suggestion that Ca^{2+} influx channels are activated in response to Ca^{2+} release from the ER was based on the assumption that reloading of the ER occurs at resting $[Ca^{2+}]_i$ (Putney, 1986). Reloading at resting $[Ca^{2+}]_i$ was shown

experimentally for the first time by direct measurement of $[Ca^{2+}]_i$ (Muallem et al., 1986) with parallel measurement of reloading the Ca^{2+} stores after their complete discharge (Muallem et al., 1986; Pandol et al., 1987) and analysis of unidirectional Ca^{2+} fluxes across the ER and plasma membrane (Muallem et al., 1988; Pandol et al., 1987). Subsequent demonstration that both passive depletion of the stores by inhibition of the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) pumps with thapsigargin and receptor stimulation activate the same Ca^{2+} influx pathway established the relationship between ER Ca^{2+} load and gating of Ca^{2+} influx channels (Takemura et al., 1989). The molecule that transmits the information of the ER Ca^{2+} load to the plasma membrane Ca^{2+} influx channels remained a mystery until the finding of STIM1 (Liou et al., 2005; Roos et al., 2005). The role of STIM1 in Ca^{2+} influx was established by demonstrating that deletion of STIM1 resulted in inhibition of Ca^{2+} influx and clustering of STIM1 at plasma membrane microdomains in response to Ca^{2+} release from the ER (Liou et al., 2005; Roos et al., 2005). This was later shown to occur in all cells examined.

STIM1 is a type 1, single transmembrane-span protein with its N-terminus in the ER lumen and its C-terminus in the cytoplasm. The N-terminus has at least two functional domains, an EF hand low affinity Ca^{2+} binding domain and a sterile alpha motif (SAM), and at least one regulatory site at cysteine 56. The EF hand Ca^{2+} binding affinity is relatively low in the range of 0.5–1 mM (Stathopulos et al., 2009) and, when bound with Ca^{2+}, traps STIM1 in the ER. Dissociation of Ca^{2+} from the EF hand results in the clustering of STIM1 at ER/plasma membrane microdomains (Liou et al., 2005; Roos et al., 2005). The SAM domain functions to facilitate clustering of STIM1 (Stathopulos et al., 2006; Stathopulos et al., 2008). STIM1 cysteine 56 is S-glutathionylated and, thus, may function as an oxidant sensor (Hawkins et al., 2010). Gating of Ca^{2+} influx channels is achieved by the STIM1 C-terminus, which opens all channels gated by STIM1 (Huang et al., 2006; Lee et al., 2010a; Yuan et al., 2009). The C-terminus starts with an ERM domain that encompasses several functional domains., the most notable of which is a minimal sequence of STIM1(344-442) termed STIM1 Orai-activating region (SOAR) (Yuan et al., 2009), CRAC (Ca^{2+}-release activating Ca^{2+} current) Activating Domain (CAD) (Park et al., 2009) or coiled-coil domain containing region b9 (CCB9) (Kawasaki et al., 2009). This domain is sufficient to fully activate the Orai channels. SOAR has a coiled-coil domain that interacts with the C-terminal coiled-coil domain of the Orais (Korzeniowski et al., 2010; Muik et al., 2009; Schindl et al., 2009; Yuan et al., 2009) to fully activate them. The CRAC-modulatory domain/Ca^{2+}-dependent inactivation (CMD/CDI) sequence is located downstream of SOAR in the Ezrin/Radixin/Moesin (ERM) domain.. The Orai channels undergo fast Ca^{2+}-dependent inactivation (Lis et al., 2007) that is mediated by the CMD/CDI patch (Derler et al., 2009; Lee et al., 2009; Mullins et al., 2009). The CMD/CDI patch interacts with a calmodulin binding site at the N-terminus of Orai1 (Mullins et al., 2009) and with conserved glutamates at the C-terminus of the three Orais to determine the isoform-specific fast Ca^{2+}-dependent inactivation (Lee et al., 2009). Downstream of the ERM domain, there are several phosphorylation sites that can be phosphorylated by several kinases and appear to control Ca^{2+} influx during mitosis (Smyth et al., 2009), although these sites have no apparent role during meiosis (Yu et al., 2009). STIM1 is also phosphorylated by Extracellular Regulated Kinase1/2 (ERK1/2), which may control interaction of STIM1 with Orai1 (Pozo-Guisado et al., 2010).

TRPC channels and STIM1

Another domain of STIM1 at end of the C-terminus is the polybasic lysine-rich domain (K-domain). The K-domain has several known roles. The K-domain anchors STIM1 to the plasma membrane and facilitates its clustering (Korzeniowski et al., 2010; Liou et al., 2007). A key function of the K-domain is gating of TRPC channels (Huang et al., 2006; Lee et al.,

2010b; Yuan et al., 2007). For a long time, TRPC channels have been considered the primary receptor-stimulated and store-operated Ca^{2+}-influx channels. (Montell, 2005; Parekh and Putney, 2005), the latter based on the findings that their downregulation and inhibition reduce SOC activity (Kiselyov et al., 2007; Villereal, 2006). The discovery of STIM1 and the Orai channels shifted attention to the Orai channels as the primary SOCs (Cahalan et al., 2007; Lee et al., 2010a). Although it is clear that Orai1 is required for all forms of Ca^{2+} influx (Lee et al., 2010a), growing evidence implicate TRPC channels in SOC and receptor-operated Ca^{2+}-influx channel (ROC) activity and in their regulation by STIM1. For example, inhibition of TRPC3 with Pyrazole 3 inhibited ROCs (Kiyonaka et al., 2009; Shirakawa et al., 2010), and inhibition of TRPC1 (Beech et al., 2003), TRPC3 (Chen et al., 2010), TRPC5 (Xu et al., 2006) and TRPC6 (Saleh et al., 2008) with anti-TRPC channel antibodies inhibited ROCs and SOCs. Knockdown by siRNA of several TRPC channels (Villereal, 2006) and gene deletion in mice of TRPC1 (Hong et al., 2010; Liu et al., 2007), TRPC3 (Kim et al., 2009) and TRPC4 (Freichel et al., 2001; Tiruppathi et al., 2002) reduced ROCs and SOCs.

Regulation of TRPC channels by STIM1 was suggested when it was discovered that TRPC1, TRPC4 and TRPC5, but not TRPC3, TRPC6 and TRPC7, interact with STIM1 and that STIM1 is required for the activity of TRPC1 (Huang et al., 2006). Subsequently, a role for STIM1 in the regulation of native and expressed TRPC channels has been demonstrated in several cell types, including the function of TRPC channels in salivary gland (Liu et al., 2007; Ong et al., 2007), vascular (Takahashi et al., 2007) and pulmonary arterial (Ng et al., 2010) smooth muscle, HL-7702 (Zhang et al., 2010), intestinal (Rao et al., 2010), mesangial (Sours-Brothers et al., 2009) and mast cells (Ma et al., 2008).

That STIM1 must be regulating channels other than Orai1 is further concluded from studying the localization of the native Orai1 and TRPC channels and the recruitment of STIM1, in particular in polarized secretory cells where Ca^{2+} signaling complexes are highly compartmentalized (Kiselyov et al., 2006). In response to store depletion, over-expressed Orai1 and STIM1 always co-cluster at the same puncta and show perfect co-localization (Huang et al., 2006; Korzeniowski et al., 2010; Liou et al., 2007; Mercer et al., 2006; Park et al., 2009; Yuan et al., 2009; Zhang et al., 2005). This is clearly not the case with the native proteins where overexpression artifacts are avoided. Orai1 is expressed almost exclusively at the apical pole of pancreatic and salivary glands acinar cells. By sharp contrast, Ca^{2+} store depletion resulted in recruitment of only a fraction of STIM1 to the apical pole, while the majority of STIM1 is recruited to the lateral pole that appears to be free of Orai1 (Hong et al., 2010). This indicates that STIM1 interacts with Orai1 and additional Ca^{2+} influx channels, which turn out to be TRPC channels since TRPC1 is also expressed at the lateral pole, deletion of TRPC1 (Hong et al., 2010; Liu et al., 2007) and TRPC3 (Kim et al., 2009) reduces SOC, and the native STIM1 co-immunoprecipitate with the native TRPC1 and Orai1. Localization and co-immunoprecipitation of the native proteins is illustrated in Fig. 2, which was taken from (Hong et al., 2010). Another recent study reported expression of small amount of Orai1 in the lateral membrane domain of acinar cells that does not express IP_3Rs (Lur et al., 2011). However, the role of this Orai1 is not known since the expression level is very low and whether STIM1 is recruited to this domain was not determined. The key finding of luminal membrane domains, identified by both Cadherin and Laminin, that do express high level of STIM1 but no Orai1 and the co-IP of STIM1 with TRPC channels in response to store depletion (Hong et al., 2010), indicates that STIM1 most likely regulates the native TRPC channels.

Opening of TRPC channels by STIM1

To address the question of the mechanism by which STIM1 opens the TRPC channels, we analyzed the role of the K-domain in TRPC channels function since deletion of the K-domain resulted in a dominant negative STIM1 inhibitor of TRPC1 (Huang et al., 2006), although the K-domain is not required for activation of Orai1 by STIM1 (Zeng et al., 2008). The K-domain likely folds as an α-helix with several positive charges at the helix surface, including the two terminal lysines (Huang et al., 2006). Deletion or mutation of the two terminal lysines also resulted in a dominant negative STIM1 that inhibits, rather than activates, TRPC1. One possibility was that the two terminal lysines of STIM1 may interact with negative charges in TRPC channels. A search for a negative patch in TRPC channels identified at least two conserved DD/E residues in the C-terminus of the TRPC channels (Lee et al., 2010b; Zeng et al., 2008). Mutational and functional analysis and complementation showed that the two terminal STIM1 lysines K684 and K685 communicate electrostatically with the conserved DD/E of TRPC channels to gate channel opening (Lee et al., 2010b; Zeng et al., 2008). These findings, therefore, indicate that STIM1 can directly gate the TRPC channels.

The sequence of the TRPC channels' C-terminal domains, where these conserved DD/E residues are located, is shown in red letters in Fig. 3A. The blue letters show the localization of the Homer ligand. Remarkably, only 4 residues separate the two sites. As outlined above, binding of Homer1 to TRPC channels and coupling them with IP_3Rs keep the channels in a closed state. Interaction of the TRPC channels' DD/E with STIM1(K684,K685) switches the channels to the open state. These findings lead to the model in Fig. 3B. The model proposes that, in the resting state, the ER is filled with Ca^{2+}, which binds to the EF hand of STIM1 to keep STIM1(K684,K685) away from the DD/E residues of the TRPC channels. The N-terminal domain of the IP_3R is in the conformation that exposes its Homer1-binding ligand to allow binding to Homer1 that also binds to the Homer1-binding ligand in the C-terminus of the TRPC channels. The TRPC-Homer-IP_3R channel complex shields the DD/E from STIM1(K684,K685). Sequestration of STIM1 in the ER and formation of the TRPC-Homer-IP_3R channel complex together ensure that the TRPC channels are kept in the closed state. Once the cells are stimulated to generate IP_3, binding of IP_3 to the IP_3Rs dissociates the IP_3R-Homer1-TRPC channel complexes. At the same time, IP_3 activates the IP_3Rs to release ER Ca2+, and dissociation of Ca2+ from STIM1 EF hand results in the clustering of STIM1 with the TRPC channels, so that now STIM1(K684,K685) can access the DD/E residues of the TRPC channels and stabilize the TRPC channels open state. As indicated throughout this review, the model in Fig. 3B is supported by multiple lines of evidence. However, the direct relationship between interaction of STIM1 and Homer1 with TRPC channels has not been explored yet. Such a study should test directly the validity of the model.

Conclusions

In this review, the molecular mechanism of gating of TRPC channels by Homer and STIM1 is highlighted. Homer binds to and couples TRPCs to IP_3Rs to keep the channels in a closed state, while STIM1 gates open TRPCs in response to depletion of ER Ca^{2+} stores. STIM1 can also regulate Orai1 channels present in the same cell type. This is exemplified best in polarized cells, where Orai1 is confined to the apical pole while TRPCs and STIM1 present in the apical and lateral membranes. The same can also be seen in other cell types. Presence of multiple store-operated Ca^{2+} influx channels in the same cells can serves to mediate selective cellular functions. An excellent recent example is the efficient activation of NFAT by Orai1-mediated, but not by TRPC-mediated, Ca^{2+} influx, while TRPC1-mediated Ca^{2+} influx activates K^+ channels and NFκB (Cheng et al., 2011).

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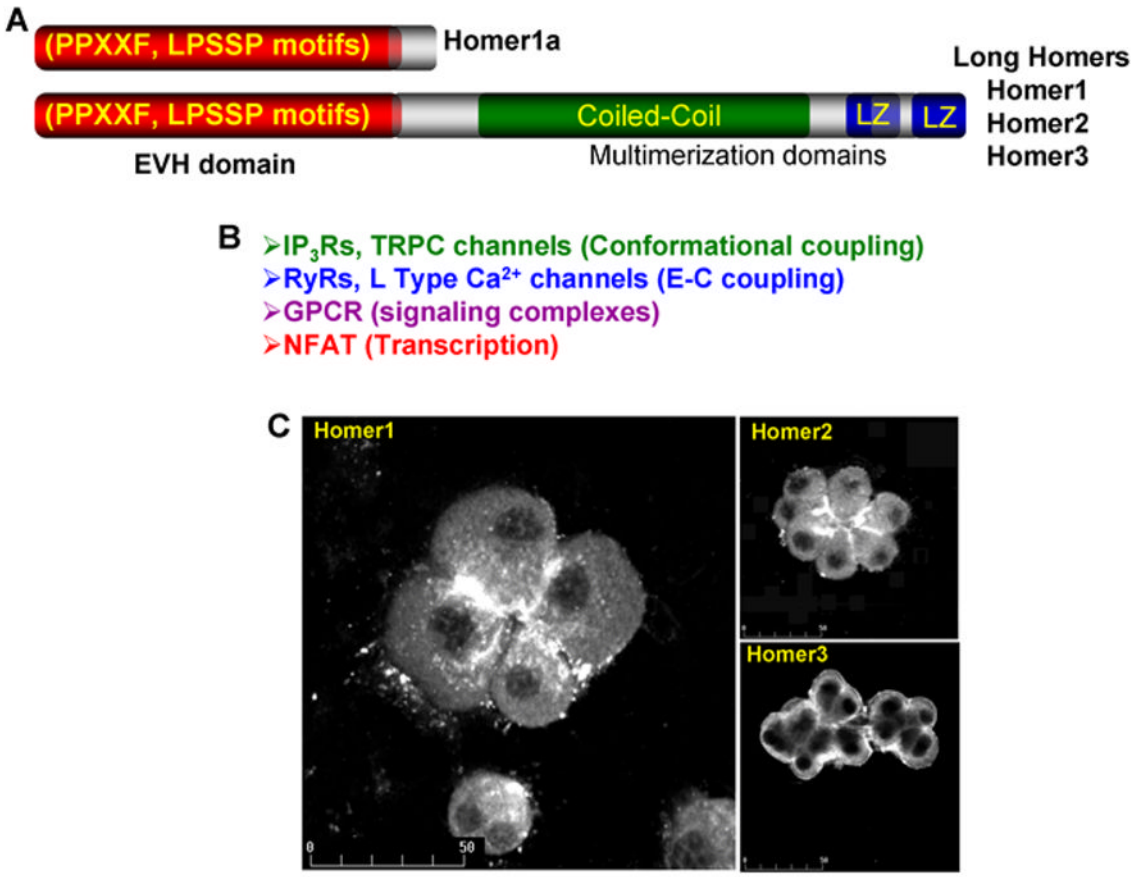

Fig. 1. The Homers and their localization

Panel (A) shows the domains of Homer1a and of the long Homers (Homer1, Homer2 and Homer3). Panel (B) lists some of the Ca^{2+} signaling proteins that have Homer ligands and have been shown to bind to the EVH domain and co-localize with the Homers. Panel (C) shows the localization of Homer1 and Homer2 at the apical pole and Homer3 in the basal pole of mouse pancreatic acini. The images in panel C were taken from (Shin et al., 2003).

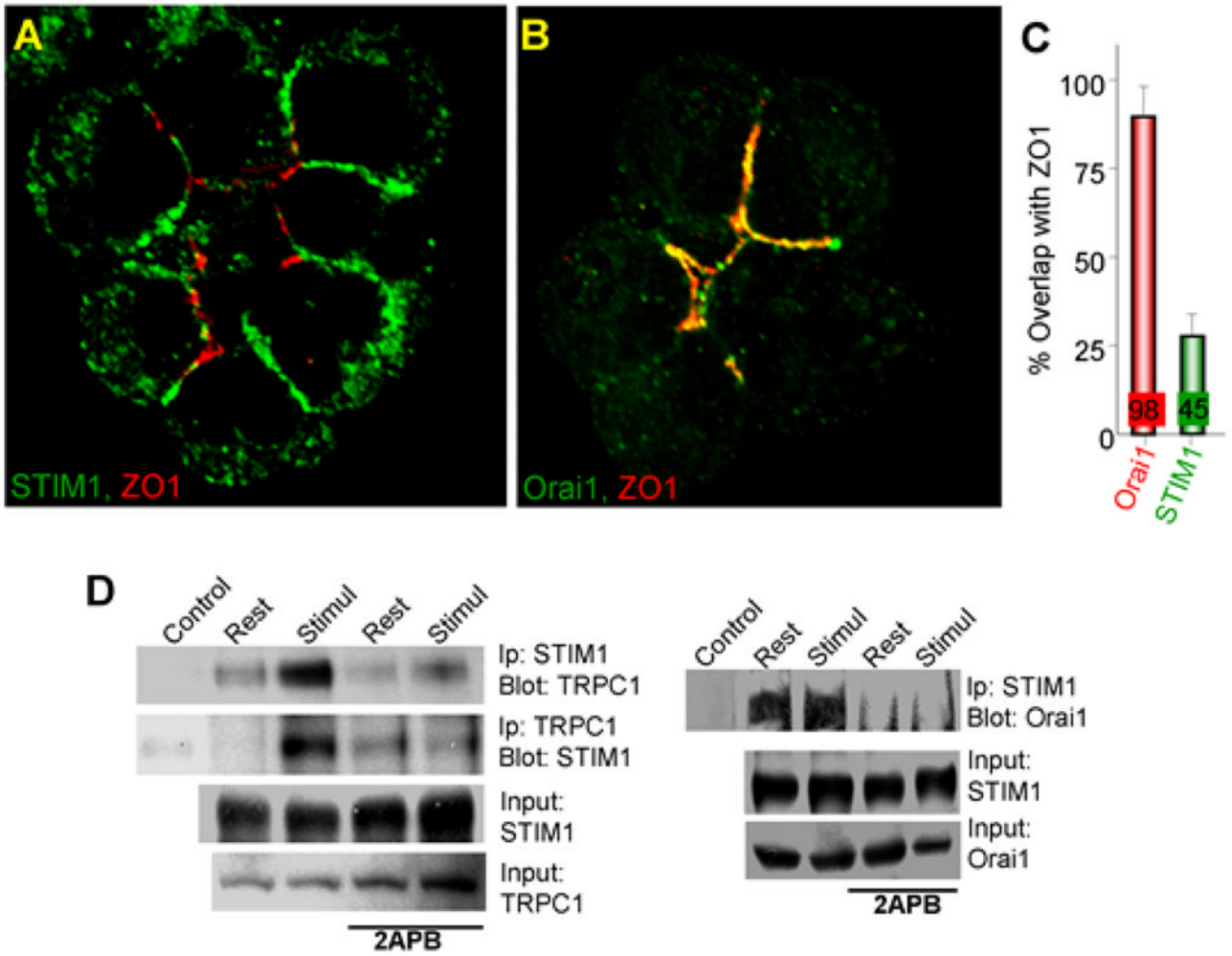

Fig. 2. Localization of *NATIVE* STIM1 and Orai1 in polarized cells

In panels (A–C), ZO1 was used to mark the tight junction at the apical pole of mouse pancreatic acinar cells. Panel (A) shows that small fraction of *native* STIM1 is at the apical pole and most of *native* STIM1 is at the lateral plasma membrane and panel (B) shows that *native* Orai1 is confined exclusively to the apical pole. The fraction of *native* STIM1 and *native* Orai1 at the apical pole is shown in panel (C). All experiments in panels (A–C) are with store-depleted cells. Panel (D) shows that *native* STIM1 and TRPC1 and STIM1 and Orai1 are co-immunoprecipitated, the co-IP of STIM1 and TRPC1 (but not of STIM1 and Orai1) is enhanced by cell stimulation that depletes the Ca^{2+} stores and the complexes are broken with 2APB, which dissociates STIM1-formed complexes. The figure is reproduced from (Hong et al., 2010).

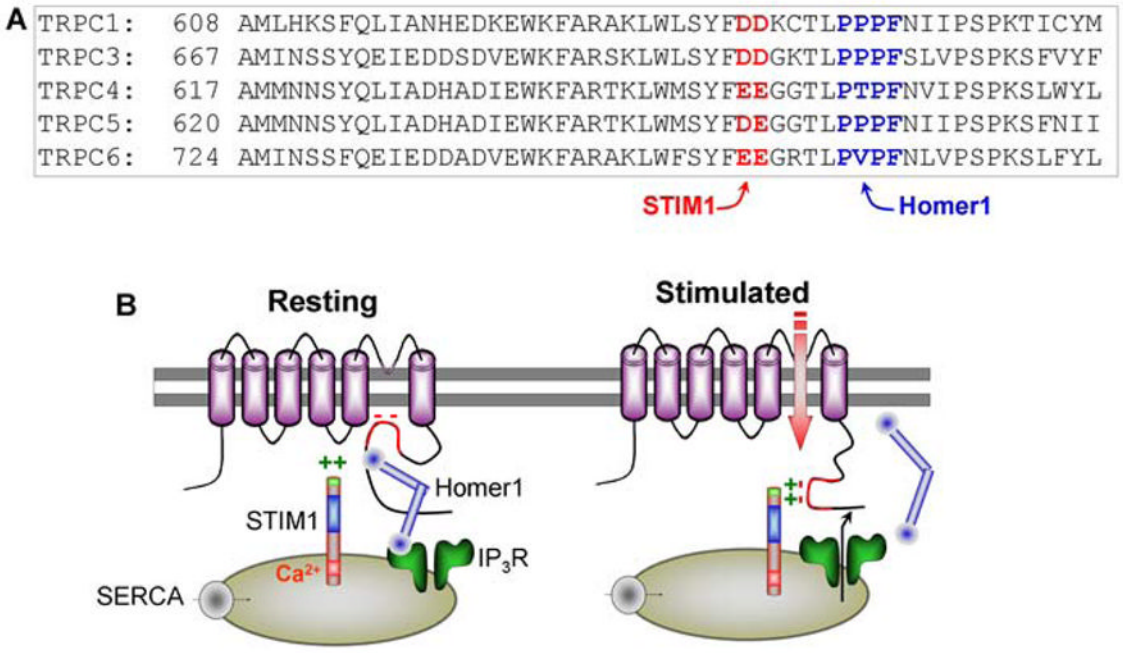

Fig. 3. A model for gating of TRPC channels by Homer1 and STIM1

Panel (A) depicts the localization of the Homer1 binding ligand (blue) and the conserved DD/E site that interacts with STIM1(K684,K685) (red) in the C-terminus of the TRPC channels. Panel (B) is a model for the proposed relationship between Homer1 and STIM1 in keeping TRPC channels in closed or open state, respectively. Further details are given in the text.