Pflugers Arch - Eur J Physiol (2007) 455:187–200
DOI 10.1007/s00424-007-0252-0

INVITED REVIEW

Organization and function of TRPC channelosomes

Indu S. Ambudkar · Hwei Ling Ong

Received: 20 January 2007 / Accepted: 10 March 2007 / Published online: 8 May 2007

Abstract TRPC proteins constitute a family of conserved Ca^{2+}-permeable cation channels which are activated in response to agonist-stimulated PIP_2 hydrolysis. These channels were initially proposed to be components of the store-operated calcium entry channel (SOC). Subsequent studies have provided substantial evidence that some TRPCs contribute to SOC activity. TRPC proteins have also been shown to form agonist-stimulated calcium entry channels that are not store-operated but are likely regulated by PIP_2 or diacylglycerol. Further, and consistent with the presently available data, selective homomeric or heteromeric interactions between TRPC monomers generate distinct agonist-stimulated cation permeable channels. We suggest that interaction between TRPC monomers, as well as the association of these channels with accessory proteins, determines their mode of regulation as well as their cellular localization and function. Currently identified accessory proteins include key Ca^{2+} signaling proteins as well as proteins involved in vesicle trafficking, cytoskeletal interactions, and scaffolding. Studies reported until now demonstrate that TRPC proteins are segregated into specific Ca^{2+} signaling complexes which can generate spatially and temporally controlled $[Ca^{2+}]_i$ signals. Thus, the functional organization of TRPC channelosomes dictates not only their regulation by extracellular stimuli but also serves as a platform to coordinate specific downstream cellular functions that are regulated as a consequence of Ca^{2+} entry. This review will focus on the accessory proteins of TRPC channels and discuss the functional implications of TRPC channelosomes and their assembly in microdomains.

Keywords TRPC proteins · Channelosomes · Channel function

I. S. Ambudkar · H. L. Ong
Secretory Physiology Section, Gene Therapy and Therapeutics Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health,
Bethesda, MD 20892, USA

I. S. Ambudkar (✉)
Building 10, Room 1N-113, 10 Center Drive, NIH,
Bethesda, MD 20892, USA
e-mail: indu.ambudkar@nih.gov

Store-operated Ca^{2+} entry: past and present

Store-operated Ca^{2+} entry (SOCE) was identified almost two decades ago as a plasma membrane (PM) Ca^{2+} entry pathway that is activated in response to depletion of Ca^{2+} in the intracellular Ca^{2+} store namely the endoplasmic reticulum (ER) [82, 84]. Although this mechanism is ubiquitously present in all cells, it has now been clearly demonstrated that distinct SOC channels are present in different cell types [2, 4, 6, 11, 14, 17, 24, 32, 45, 46, 48, 66, 75, 76, 119, 127]. However, neither the molecular components of these channels nor the mechanism(s) that signals the ER-$[Ca^{2+}]$ status to the PM channel have yet been conclusively established in all cell types. The well-established role of *Drosophila* TRP channel in phototransduction [62, 65] propelled the search for molecular components of SOC channels and led to the identification of mammalian TRPC channels. Studies with TRPCs have primarily been focused on demonstrating their involvement in SOCE, and data obtained over the past 10 years or so provide strong evidence that TRPC channels critically contribute to SOCE in a number of different cell types. In addition, these studies also provided evidence for TRPC channel contribution to agonist-dependent, store-independent Ca^{2+} channels [for reviews, see 2, 4, 6, 62, 65, 76,

115]. In this chapter, we will first briefly review SOCE, including the recent advances in this area, and then focus on the accessory proteins of TRPC channels and the functional implications of TRPC channelosomes.

Early observations that SOCE-dependent refill of internal Ca^{2+} stores occurred without significant increase in $[Ca^{2+}]_i$ [60, 82, 84, 103] lead to the suggestion that this Ca^{2+} entry occurs in specific cellular domains within which Ca^{2+} entering the cell is rapidly sequestered into the ER by the activity of the ER Ca^{2+} pump (SERCA), with minimal diffusion of Ca^{2+} in the cytosol [47, 59, 63, 64]. Thus, it was proposed that the ER is closely apposed to the PM at the site of SOCE. The recognition of such domains provided the basis for several models proposed for the activation of SOCE [11, 34, 78, 84–86]. The models that have received most attention are: (1) "conformational coupling", which suggests close physical association between the PM Ca^{2+} channel and an ER protein that can detect and relay the luminal $[Ca^{2+}]$ status to the surface membrane; (2) "secretion coupling", according to which, cortical ER is dynamically regulated so that it interacts with PM channels when luminal $[Ca^{2+}]$ is low; (3) "recruitment of channels", which suggests regulated trafficking and fusion of channel-containing vesicles with the PM in response to store depletion; and (4) "diffusible messenger", which suggests that a diffusible calcium influx factor is generated in response to ER-Ca^{2+} depletion and released into the cytosol, resulting in the activation of the PM Ca^{2+} channel. While there are insufficient data to conclusively prove or discard any of these models, recent developments in this field (described below) provide strong evidence in support of the first two models. It is also important to note that these new data suggest that these models need not be mutually exclusive.

Three of the four models for SOCE activation predict, and have a requirement for, close proximity of PM and ER. Consistent with this, functional, biochemical, and morphological data reveal the presence of junctional domains in cells formed by components of PM and peripheral ER within which Ca^{2+} signaling and Ca^{2+} entry occur [1, 2, 7, 38, 39, 63, 84]. There is now general consensus that SOC channels, as well as Ca^{2+} signaling proteins including upstream components such as G protein-coupled receptors, G-proteins and phospholipase C (PLC), and downstream components such as inositol trisphosphate receptors (IP_3Rs) as well as $[Ca^{2+}]_i$ regulatory proteins such as SERCA and PMCA are assembled in a supramolecular signaling complex [2, 38, 39, 41]. In addition, non-protein PM components such as PIP_2 and PIP_3, which are critically involved Ca^{2+} signaling, are also localized in these junctional microdomains. Notably, these lipids, as well as cholesterol and sphingolipids, are concentrated in biochemically distinct PM lipid domains called lipid raft domains (LRD) or caveolar LRD, referring to LRD that contain the cholesterol-binding protein caveolin-1 [1, 35, 94]. As key Ca^{2+} signaling protein complexes have been found in caveolar LRD (also called caveolae) and disruption of these domains attenuates SOCE, these domains have been suggested to provide a platform for the Ca^{2+} signaling mechanisms (further discussed below). Thus, proteins involved in generating the $[Ca^{2+}]_i$ signal, as well as those regulating the level of $[Ca^{2+}]_i$ in the cell, are tightly associated with each other. More importantly, there is dynamic remodeling of this complex and recruitment of regulatory proteins when cells are stimulated [30, 36, 57, 73, 79, 90, 126]. Rearrangements of the local cytoskeleton and microtubule network have been implicated in the regulation domain architecture, e.g., increase in cortical actin due to hyperpolymerization of actin decreases SOCE [78, 89, 90]. Although it has been proposed that this decrease is due to cortical actin forming a physical barrier between the ER and PM, key Ca^{2+} signaling proteins from the PM, and caveolae, are internalized under these conditions [4, 50, 94]. Such internalization is indicative of the involvement of vesicular trafficking mechanisms which are regulated by cytoskeletal rearrangements as well as by changes in PM levels of PIP_2 and PIP_3 [8, 21, 28]. The role of vesicular trafficking, which is emerging as a key mechanism in the regulation of agonist-stimulated Ca^{2+} entry channels, is further discussed below.

Recent studies have provided novel insights into a possible mechanism for regulation of SOC channels. A key finding is the clustering of Ca^{2+} signaling proteins in response to stimulation of cells and depletion of internal Ca^{2+} stores. IP_3R is a central protein in Ca^{2+} signaling and regulation of SOC channels [7, 30, 38, 39, 77, 78, 85, 115] despite contradictory reports regarding its role in SOCE [55, 113]. Consistent with its proposed role in SOCE regulation, IP_3R undergoes clustering in the peripheral region of the ER, the location of which has been suggested as the ER–PM interaction zone involved in activation of SOCE [30]. The stromal interacting molecule 1 (STIM1), an ER Ca^{2+} sensor protein previously described as a tumor suppressor protein, has now been proposed as a regulatory protein for Ca^{2+} release-activated Ca^{2+} (CRAC) channels (which mediate SOCE in T lymphocytes and other hematopoietic cells) as well as SOCE in several other cell types [88, 97]. More significantly, STIM1 also undergoes clustering in the subplasma membrane region in response to agonist stimulation and intracellular Ca^{2+} store depletion. There are convincing data to show that Ca^{2+} entry via CRAC channels occurs at the site where these STIM1 clusters are formed [44, 53, 129]. Further, STIM1 and IP_3R are recruited to a PM–SOC channel complex by a cytoskeleton-dependent mechanism after store depletion in platelets [52]. Thus, although it is not clear whether STIM1

and IP_3R co-cluster, the "clusters" can be suggested to represent centers where dynamic remodeling of protein complexes occurs during regulation of SOCE. Such rearrangement is reminiscent of other Ca^{2+} channel complexes such as the glutamate receptors which are reorganized into clusters within specific PM regions in the post-synaptic membrane of neuronal cells in response to stimulation [27, 69]. It is also important to note that depletion of Ca^{2+} in the peripheral ER Ca^{2+} store is sufficient for STIM1 clustering and likely is the determining factor for activation of Ca^{2+} entry [73]. Thus, the entire mechanism involved in mediating and regulating Ca^{2+} entry are contained within junctional domains that involve peripheral ER and PM.

As mentioned above, the molecular components of store-operated and store-independent calcium channels have not yet been conclusively established. Substantial data demonstrate that all members of the TRPC family of cation channel proteins are activated by agonist-stimulated PIP_2 hydrolysis, although only some TRPCs contribute to SOCE [2, 6, 65, 76, 83, 98, 115, 117]. It has been recently reported that a four-transmembrane PM protein, Orai1, together with STIM1, is sufficient for generation of CRAC channels [81, 116, 123]. However, the role of Orai1 in SOC channels found in other cell types has not yet been demonstrated. Significantly, it has now been demonstrated that TRPC1-dependent SOC channels are also regulated by STIM1 [32, 52, 72] and that several TRPCs interact with STIM1 [32]. More intriguingly TRPC1, Orai1, as well as STIM1 appear to contribute to SOCE [72] in a human salivary gland cell line. These recent studies provide novel molecular insights on how distinct SOC channels might be assembled. The rest of this review will focus on TRPC channelosomes and how accessory proteins might determine their function.

Role of TRPC-cation channels in agonist-stimulated Ca^{2+} entry

It is well recognized that activation of cell surface receptors which are coupled to inositol lipid signaling results in PIP_2 hydrolysis, generation of diacylglycerol (DAG) and IP_3, release of Ca^{2+} from internal Ca^{2+} stores, and activation of PM Ca^{2+} influx channels. Studies with TRPC proteins have revealed that agonist-generated signals can activate two major types of Ca^{2+} entry. SOCE, which, as described above, depends on the depletion of Ca^{2+} from the internal Ca^{2+} stores rather than PIP_2 hydrolysis per se. The characteristics of the currents activated by store depletion in cells such as T lymphocytes, RBL, salivary gland, endothelial, and smooth muscle cells have demonstrated the presence of different types SOC channels ranging from non-selective to very Ca^{2+} selective [4, 11, 46, 65, 76, 83, 91, 98, 117]. There is convincing evidence for the contribution of TRPC1 and TRPC4 to SOC channels [17]. TRPC3 and TRPC7 have also been shown to generate SOC when they are in a complex with TRPC1 [45, 127]. Although the physiological significance of such diversity in SOCs is not clear, it is important to consider whether all these channels are activated by the same signal generated in response to internal Ca^{2+} store depletion or whether internal Ca^{2+} store depletion induces multiple intracellular signals that act on different channels. TRPCs also contribute to "second messenger-operated channels" (SMOCs) that are activated by receptor-stimulated PIP_2 hydrolysis but do not depend on internal Ca^{2+} store depletion. These channels are most likely either directly activated by DAG or by PIP_2 hydrolysis per se [1, 2, 65, 76, 83, 98]. TRPC3, TRPC6, and TRPC7 have been shown to be activated by DAG [19, 83]. An important question that arises is how cells coordinate signals generated in the PM and within the same Ca^{2+} signaling cascade, with the activation of different Ca^{2+} channels. As has been described for several ion channel complexes, this is achieved by segregating the proteins into complexes allowing the channel to be located in close proximity to its regulator. Such an organization determines not only the specificity of interactions but also the rate of signal transduction. Further, segregating these protein complexes into required cellular domains allows for the generation of compartmentalized Ca^{2+} signals [1, 2, 38, 39, 65] which can be locally decoded for regulation of downstream effectors. Thus, resolving the organization of agonist-stimulated Ca^{2+} signaling microdomains is critical for understanding how cells distinguish different Ca^{2+} signals to regulate specific Ca^{2+}-dependent cellular function.

Although there has been intense focus on TRP channels over the past decade, conclusive data regarding the exact physiological function of most of these channels are still lacking. Part of this is due to conflicting data regarding their activation mechanisms. These discrepancies stem from the use of heterologous expression systems and the lack of specific pharmacological tools to affect channel properties. Despite this, there are sufficient data to demonstrate that TRPCs form distinct channels that not only differ in their biophysical characteristics but also in their modes of activation [65, 76, 100]. Studies with TRPCs (both endogenously and exogenously expressed) demonstrate homomeric and heteromeric interactions between TRPC monomers (Table 1). Most of the reported interactions appear to involve the N-terminus of the channels and, more specifically, the coiled-coiled or ankyrin repeat regions of the protein [22, 31, 40, 45, 92, 117]. More detailed studies will be required to map the exact residues involved. It is important to note that heterogenously expressed proteins could interact promiscuously with other endogenously expressed TRPC monomers or exhibit different modes of activation depending on their level of expression, e.g.,

Table 1 TRPC binding partners

TRPC1	TRPC2	TRPC3	TRPC4	TRPC5	TRPC6	TRPC7
TRPC1[b] [100]		TRPC1[b] [43, 100, 119, 127]	TRPC1[b] [17, 31, 100, 101]	TRPC1[b] [100, 101]		TRPC1[b] [127]
	TRPC2[a] [31]				TRPC2[b] [13]	
TRPC3[b] [43, 100, 119, 127]		TRPC3[a] [31]			TRPC3[b] [5, 31, 45, 100]	TRPC3[b] [127]
TRPC4[a,b] [17, 31, 100, 101]			TRPC4[a] [31]	TRPC4[a] [31]		
TRPC5[b] [100, 101]			TRPC5[a] [31]	TRPC5		
	TRPC6[b] [16]	TRPC6[a,b] [5, 31, 45]			TRPC6[a] [31]	TRPC6[b] [48]
TRPC7[b] [127]		TRPC7[b] [127]			TRPC7[b] [48]	TRPC7

References are as indicated in brackets.
[a] Indicates interactions observed in studies with heterologously expressed proteins
[b] Indicates interactions observed in studies with endogenous proteins

TRPC3 displays store-dependent activation when expressed at low levels and store-independent activity at higher levels of expression [114]. Thus, meaningful conclusions regarding the type of channel formed by specific TRPC protein(s) and its physiological function can only be based on data with the endogenous proteins. The number of studies assessing the function of the endogenous proteins, mostly using a knock-down approach, is steadily increasing, and the data available until now clearly demonstrate the capacity of TRPCs to form diverse channels [reviewed in detail in 4, 55, 76, 91, 117]. Further, all TRPC proteins have been shown to be closely associated with a number of accessory proteins that appear to be involved not only in the regulation of channel function but also in their cellular localization and PM expression [2, 38, 65]. These include key Ca^{2+} signaling proteins as well as

Table 2 TRPC channelsomes

TRPC1	TRPC2	TRPC3	TRPC4	TRPC5	TRPC6	TRPC7
IP_3R [51, 57, 90]	IP_3R [109]	IP_3R [5, 37, 50]	IP_3R	IP_3R	IP_3R	IP_3R
CaM [51]	CaM	CaM	CaM	CaM [74]	CaM [12]	CaM
Gq/11 [51]		Gq/11 [5, 50]			Gαq/11	
PLCβ [51]	PLCβ	PLCβ [5, 50]	PLCβ [62, 105]	PLCβ [105]	PLCβ	PLCβ
GPC or TrkR		GPC or TrkR			GPC or TrkR	
STIM1 [32, 52, 72]	STIM1 [32]		STIM1 [32]			
	Junctate [99]	Junctate [99]			Junctate [99]	
PMCA [38, 39, 50]		PMCA	PMCA	PMCA	PMCA	
SERCA		SERCA [50, 38, 39]			SERCA	
Enkurin [102]	Enkurin [102]			Enkurin [102]		
	PLCγ [109]	PLCγ [79]		PLCγ	PLCγ	
Homer [126]		Homer [37]				
			NHERF [61, 105]	NHERF [61, 105]		
			ZOI [105]	ZOI [105]		
Caveolin [1, 13, 51]		Caveolin [50]	Caveolin	Caveolin		
MxA [54]	MxA [54]	MxA [54]	MxA [54]	MxA [54]	MxA [54]	MxA [54]
RhoA [57]				RhoA	RhoA	
SNARES [89]		SNARES [95]		SNARES [8, 26]		

Only proteins common to 2 or more TRPCs have been listed. Components involved in Ca^{2+} signaling are shown in the top half of the table, the bottom half of the table show interacting proteins involved in scaffolding and trafficking. References are as indicated in brackets and superscript.

proteins involved in vesicle trafficking, cytoskeletal interactions, and scaffolding (see Table 2). These findings suggest that TRPC proteins are segregated into specific Ca^{2+} signaling complexes.

TRPC channelosomes and regulation of channel function

The *Drosophila* TRP and TRPL channels are assembled in a Ca^{2+} signaling complex via their interaction with INAD, a multi-PDZ domain containing scaffolding protein [62, 65]. INAD binds to a number of signaling proteins, such as calmodulin (CaM), PLC, G-protein, and protein kinase C (PKC), which are involved in channel activation, inactivation, and regulation. Similarly, as shown in Table 2, mammalian TRPCs are also assembled in protein complexes. In addition, since TRPC channels have the inherent ability to form homomeric and heteromeric channels, selective association between them can generate a plethora of channel types. Thus, it can be proposed that the components of TRPC signalplexes determine not only the type of channel that is formed but also the cellular localization and targeting of these signalplexes. The rest of this review will focus on the accessory proteins of TRPC proteins and functional implications of TRPC channelosomes.

TRPC1 TRPC1 is currently the strongest TRPC candidate for SOC [see 1, 4, 6, 49, 65, 76, 91 for recent reviews]. The characteristics of the channels formed by TRPC1 are quite diverse, ranging from relatively Ca^{2+} selective to non-selective (Ca^{2+} vs Na^{+}) depending on their molecular composition [4, 6, 14, 17, 45, 48, 66]. TRPC1 is suggested to have a role in various physiological functions, including fluid secretion, endothelial cell migration and permeability, smooth and skeletal muscle function, cell proliferation, differentiation, wound healing, and protection against cell death [4, 6, 10, 87, 91]. Surface expression of TRPC1 appears to depend on its interactions with other TRPCs (e.g., TRPC1, TRPC4) [17, 22, 31] or other proteins such as caveolin-1 [1, 13], β-tubulin (microtubule structures) [9], and RhoA (remodeling of the cytoskeleton) [57]. TRPC1 interaction with caveolin-1 and RhoA mediates its localization in caveolae. In addition, the TRPC1-signalplex also contains key Ca^{2+} signaling proteins such PLC, $G_{\alpha q/11}$, IP_3R [51, 126] and depending on the cell type, neurotransmitter and growth factor receptors such as bradykinin [18] and fibroblast growth factor receptors [23]. Most of these proteins are involved upstream in the signaling cascade, leading to PIP_2 hydrolysis, IP_3 generation, and release of Ca^{2+} from the ER, i.e., events that result in the activation of Ca^{2+} entry.

A major focus has been placed on IP_3R, which was first described as the ER protein involved in the activation of SOCE [34, 85]. There is convincing evidence that IP_3R regulates TRPC1 function. The scaffolding protein HOMER has been suggested to mediate the interaction between TRPC1 and IP_3R, and disruption of this interaction is associated with TRPC1 activation by ER-Ca^{2+} depletion [126]. In contrast, an increase in association of IP_3R with TRPC1 has been seen in platelets and endothelial cells, suggesting that the IP_3R-TRPC1 interaction is required for SOCE [52, 57, 90]. Recently, as discussed above, STIM1 has been proposed to function as a regulator for SOCE. The C-Terminus of STIM1 interacts with and activates TRPC1 [32]. Further, Lopez et al. [52] recently reported that TRPC1 forms a complex with IP_3RII and STIM1 in human platelets and that after store depletion, there is increased interaction between these proteins. Thus, HOMER and STIM1 mediate very different effects on TRPC1-IP_3R interactions, although both induce activation of SOCE. RhoA has also been shown to mediate TRPC1–IP_3R interactions in endothelial cells and regulate SOCE [57]. In this case, a ternary complex is formed upon stimulation, which results in increased TRPC1 in the PM. While HOMER does not affect the level of TRPC1 in the PM, the effect of STIM1 on TRPC1 surface expression is not yet known. We have recently reported that TRPC1 associates with Orai1 [72]. Further, we showed that Orai1, TRPC1, and STIM1 concertedly regulate SOCE. Stimulation with calcium-depleting agents increases the association between these proteins. Thus, a ternary complex of TRPC1, Orai1, and STIM1 determines SOCE in cells where TRPC1 was previously shown to contribute to SOCE. More importantly, these data demonstrate that Orai1 is required for TRPC1-mediated SOCE. The status of IP_3R, and whether it interacts with Orai1, has not been assessed in this study. Thus, further studies will be required to clarify the role of IP_3R in TRPC1 function and to identify the components of TRPC1-channelosome that are involved in trafficking per se and those that directly regulate the gating and function of the channel.

TRPC2 There is relatively less known about TRPC2 compared to other TRPCs. While the mouse and bovine TRPC2 genes form functional channels, TRPC2 is not expressed in human tissues [43, 124], but is abundantly found in the vomeronasal organ (VNO) of rodents. Mouse TRPC2 has been shown to mediate pheromone sensory signaling and TRPC2−/− mice exhibit defective sexual and social behaviors [43, 132]. The interaction of TRPC2 with other TRPCs have not been fully investigated, although one study showed that TRPC2 did not interact with any TRPCs when heterologously expressed in HEK293 cells [31]; another showed that TRPC2 interacts with endogenous TRPC6 in primary erythroid cells [16]. Nonetheless, TRPC2 has been shown to form a signalplex with erythropoietin receptor, IP_3RIII and PLCγ [109]. Enkurin,

which is also highly expressed in testis and VNO, interacts with TRPC2. Enkurin contains binding sites for calmodulin and SH3 domain proteins, such as the p85 regulatory subunit of PI3K, and thus, has been proposed to function as an adaptor that localizes TRPC2 and other regulatory proteins in a signalplex [102]. In addition, the C-terminus of TRPC2 binds to the N-terminus of junctate, which might determine its regulation by store depletion in some cell types [99]. TRPC2 also binds to STIM1 [32].

TRPC3 TRPC3, TRPC6, and TRPC7 are grouped together based on the considerable homology in their amino acid sequence and in their mode of activation [19, 65, 83, 98]. Nonetheless, the physiological properties and functions attributed to TRPC3 are quite distinct from those of TRPC6 and TRPC7. TRPC3 can form both store-independent and store-dependent channels in different cell types [45, 83, 98, 119, 127], and this has been suggested to depend on the level of protein expression. High levels of expression results in homomeric TRPC3 channels with constitutive store-independent activity, whereas low channel expression results in store-dependent activity [114]. As TRPC1 + TRPC3 [45], and also TRPC1 + TRPC3 + TRPC7 [127], interactions have been reported in generation of SOC channels, the exact molecular interactions involved in generation of TRPC3-SOC channels need to be further examined. It is possible that when low levels of TRPC3 are expressed, it can interact with endogenous TRPC1 to form SOC channels (see Fig. 1). Localization of TRPC3 in the PM depends on the status of actin [50], while its calmodulin/IP_3 receptor-binding (CIRB) region is involved in targeting the channel to the PM [118]. Interaction with PLCγ regulates TRPC3 cell surface expression and facilitates interaction or anchoring of TRPC3 with the PM lipid, PIP_2. Interestingly, TRPC3–PLCγ–PIP_2 interaction does not appear to be required for its activation, but rather for channel retention in the membrane and cell surface expression [79]. We reported that PM expression of TRPC3 is dependent on vesicular trafficking and mediated via its interaction with the vesicle soluble NSF attachment receptor (SNARE) protein, VAMP2. Both constitutive and regulated trafficking mechanisms were identified; the former was Ca^{2+}-dependent, while the latter was dependent on PIP_2 hydrolysis, but not on intracellular [Ca^{2+}] increase [95]. Similarly, HOMER has been shown to mediate the interaction between IP_3R and TRPC3, and these interactions determine the rate of TRPC3 translocation to and retrieval from the PM [37]. TRPC3 also interacts with

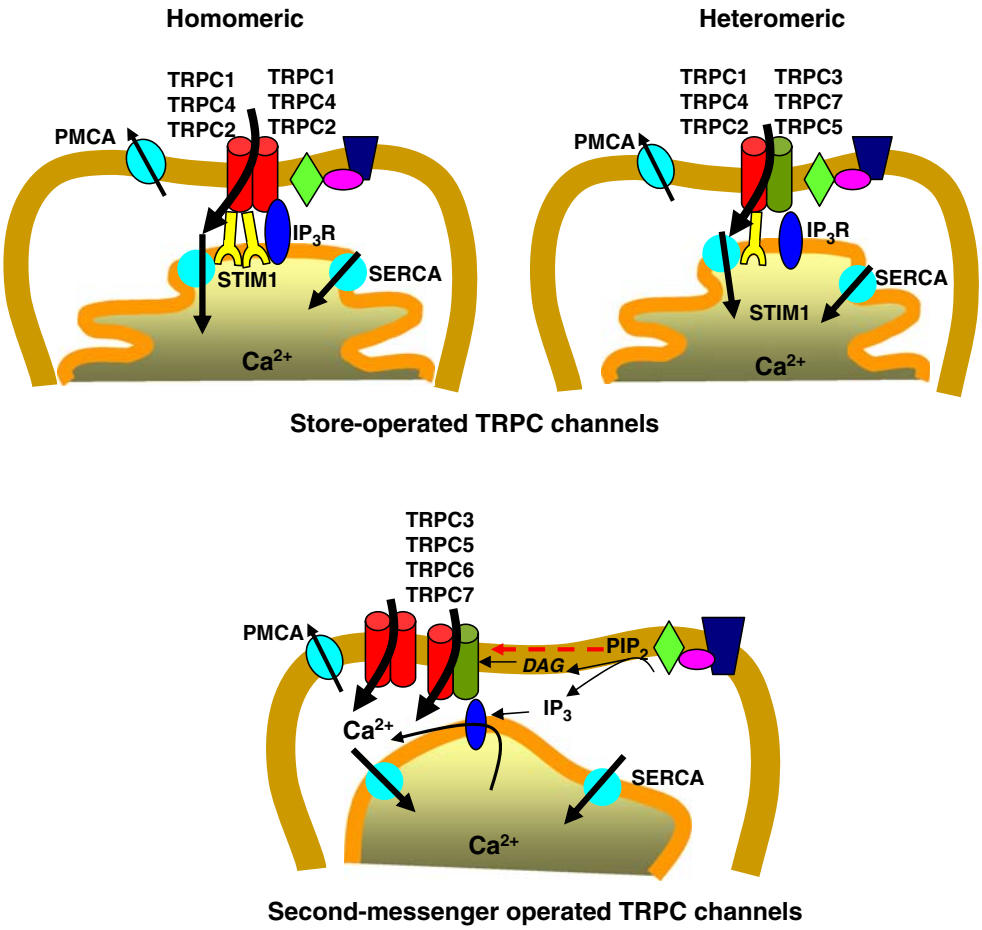

Fig. 1 Possible arrangement of TRPC monomers and accessory proteins in the formation of SOCs (*top two illustrations*) or non-SOC (*bottom illustration*). Although only G protein-coupled receptor has been shown, receptor tyrosine kinases also activate TRPC channels. The model is further explained in the text (also see Tables 1 and 2 for details on the interactions of TRPC proteins with other TRPCs as well as with accessory proteins)

MxA, a member of the dynamin superfamily [54], and this interaction is most likely involved in trafficking of the channel. However, the exact components of the TRPC3 channelosome that are involved in constitutive and regulated trafficking of TRPC3, as well as its ability to generate SOC channels, have not yet been resolved.

TRPC4 TRPC4 is most closely related to TRPC5, sharing 73% amino acid identity, but both proteins diverge in the last 220 amino acids. Studies with TRPC4−/− mice models have implicated TRPC4 in endothelial cell function and vascular smooth muscle contractility [24], lung microvascular permeability [108], and corneal epithelial cell proliferation [122]. While there is general consensus that TRPC4 forms a store-dependent channel [65, 76], some studies show that it forms constitutively active or store-independent channels [80]. TRPC4 interacts with the PDZ domain proteins NHERF and ZO1 via the "VTTRL" sequence in the C-Terminus [105]. It also interacts with PLCβ [61] and the protein tyrosine kinase, fyn [71]. The dynamic interplay between tyrosine kinases, TRPC4, and NHERF regulates PM expression and activation of TRPC4 channels. EGF stimulation induces fyn-dependent phosphorylation of TRPC4, which increases its interaction with NHERF and activates its exocytotic insertion into the PM [71]. Interestingly, TRPC4 is also associated with caveolae [110] where growth factor receptor signaling proteins as well as NHERF-binding proteins such as ezrin are localized. It has been suggested that the interaction with NHERF and Z01 provide a scaffold to position the channel in the apical or lateral regions of polarized cells such as endothelial cells. TRPC4 also interacts with STIM1, consistent with its store-dependent regulation [32].

TRPC5 Although TRPC5 shares significant homology with TRPC4, its localization, physiological function, and properties differ greatly. TRPC5 has been reported to form both store-operated and store-independent channels and form multimeric channels with TRPC1 and TRPC4 [80, 101, 120, 128]. It is predominantly expressed in the brain where it appears to have a significant role in regulating neuronal growth [26, 33]. Like TRPC4, TRPC5 also has the sequence "VTTRL" in the C-Terminus, which mediates its interaction with PDZ-binding proteins such as NHERF and ezrin/moesin/radixin-binding phosphoprotein 50 (EBP50) [70, 105]. Interaction with NHERF mediates its association with PLCβ and regulates surface expression of TRPC5, whereas interaction with EBP50 links the channel to the cytoskeleton via ezrin and modulates the activation kinetics of TRPC5 after agonist stimulation. Further, a recent study also showed TRPC5 interaction with cytoskeletal proteins such as actinin, actin, and drebrin [25]. In addition to the "VTTRL" motif, two CaM binding sites located in the C-terminus of TRPC5 have been reported [74, 104]. Both CaM binding sites are involved in modulating channel responses to agonist stimulation. Myosin light chain kinase and PKC have also been shown to regulate TRPC5 function, although it is not clear whether this involves direct effects on TRPC5 or is mediated via regulation of the cytoskeleton [93, 130]. Trafficking of TRPC5 to specific sites in the hippocampal neurons is determined by its interaction with the exocyst component protein stathmin-2, which targets the homomeric channel to the growth cone of hippocampal neurons [26]. SNARE proteins have also been found to be associated with the TRPC5-trafficking complex. TRPC5 is localized in vesicles with proteins involved in vesicle trafficking such as dynamin, clathrin, and MxA [25, 26], suggesting that TRPC5 trafficking may involve endocytosis via clathrin-coated pits. Rapid trafficking of these vesicles to the PM is activated in response to stimulation of hippocampal and other neuronal cells with EGF and NGF, with relatively weaker responses to BDNF and GF-1 [8]. Incorporation of the channel into the PM also involves PI3K, the GTPase, Rac1, as well as PI4K. Ca^{2+} entry via the TRPC5 channel inhibits extension of growth cones, but the exact mechanisms mediating this inhibitory effect are not yet known [26]. Recently, Hui et al. [33] showed that the neuronal calcium sensor-1 (NCS-1) binds to the C-terminus of TRPC5, and the TRPC5-NSC-1 protein complex was shown to retard neurite outgrowth. Interestingly, while TRPC1 + TRPC5 heteromers are localized in neurites and TRPC5 homomers are found in the growth cones, only the latter has an effect on the elongation of the growth cone [8]. TRPC5 has also been linked to vascular smooth muscle cell motility after activation of the TRPC1 + TRPC5 channel by sphingosine-1-phosphate [121]. Thus, components of the TRPC5 channelosome reveal the molecular basis for its trafficking, internalization, and cellular function. Further, these findings also substantiate the ability of TRPC proteins to generate functionally distinct calcium channels.

TRPC6 TRPC6 shares close sequence and structural homology with TRPC3 and TRPC7, and has been unequivocally shown to be activated by DAG and not by internal Ca^{2+} store depletion [19, 83]. It has been associated with epinephrine-evoked Ca^{2+} entry in smooth muscle cells from rat portal vein [19] and arginine vasopressin-induced Ca^{2+} entry in vascular smooth muscle cells [56]. TRPC6−/− mice show increased vascular smooth muscle contractility [20], which is due to a compensatory increase in spontaneously active TRPC3 channels. TRPC6 channels are also involved in the growth of pontine neurons (TRPC3 + TRPC6) [42] and prostate cancer epithelial cells [106]. TRPC6 translocates to the PM upon stimulation with muscarinic agonists by a Ca^{2+}-independent mechanism [15]. The tyrosine kinase, fyn, an

accessory protein for TRPC6, has been suggested to regulate channel activation, but it is not clear whether phosphorylation has a role in TRPC6 translocation [29].

Relatively less is known about proteins that interact with and regulate the trafficking and activity of TRPC6, although TRPC6 has been shown to bind to enkurin [102], cytoskeletal proteins such as actinin, actin, and drebrin [25] and endocytic vesicle-associated proteins such as dynamin, clathrin, and MxA [25, 54] and the plasmalemmal Na+/K+ ATPase pump [25]. Further, TRPC6 also contains conserved IP_3R- and CaM-binding domains, and CaM reportedly regulates TRPC6 activation [12]. While cytoskeletal proteins can potentially exert an effect on channel trafficking, the role of these proteins in TRPC6 trafficking has not been directly demonstrated. In addition, after stimulation with carbachol, several proteins including PKC and the muscarinic receptor are recruited to TRPC6 [36]. It is important to recognize that both TRPC3 and TRPC6 are regulated by PIP_2 hydrolysis and undergo translocation to the PM in response to agonist stimulation. Furthermore, TRPC6 has been shown to co-immunoprecipitate with TRPC3 and TRPC7 [5, 31, 56]. However, any direct impact of TRPC multimerization on TRPC6 trafficking is not yet known. It is also not clear whether trafficking of homomeric channels differs from that of heteromeric channels. This might be an important consideration for all TRPCs.

TRPC7 TRPC7 was first isolated from fetal brain and caudate nucleus cDNA libraries and was predominantly expressed in different regions of the brain such as the cerebral cortex, occipital pole, and amygdala [67]. The TRPC7 gene maps to the human chromosome 21q22.3 and has been proposed to be a candidate gene for genetic disorders. TRPC7 gene expression is significantly lower in B lymphoblast cell lines obtained from patients with bipolar disorders [125]. When compared to the other TRPCs, less is known about TRPC7, although store-dependent and –independent, as well as constitutive activation, have been observed [19, 83]. Importantly, TRPC7 was shown to generate SOC channels when it interacts with TRPC1 and TRPC3 in HEK293 cells [127]. In addition to its interaction with TRPC6, TRPC7 has been reported to interact with MxA [54], but how this interaction affects TRPC7 trafficking and channel activity has not been investigated.

Functional implications of TRPC channelosomes

Type of channel As discussed above, interaction of TRPC monomers results in the generation of biophysically distinct homomeric or heteromeric channels all of which are relatively non-selective for Ca^{2+} (vs Na^+), with the exception of TRPC4 and TRPC1. These channels are also regulated differently, e.g., TRPC1 + TRPC3 form SOC channels [45, 119] while TRPC3 + TRPC6 generate store-independent, DAG-activated, channels [107], and TRPC3 monomers appear to be spontaneously active [20, 83]. Thus, TRPC3, depending on its interacting partner, can form different types of Ca^{2+} entry channels. It is very likely that the type of channel that is formed is determined by the associated regulatory protein. An ER-Ca^{2+} sensor protein STIM1, which has been proposed to relay the internal Ca^{2+} store status to the PM channel and to be the key regulator of SOCE, interacts with the TRPC channels that currently are the strongest candidates for SOC, i.e., TRPC1 and TRPC4 [32, 52, 72]. Note that STIM1 also interacts with TRPC2, which, although not expressed in human cells, has been shown to be regulated by store depletion [32]. In contrast, store-independent SMOC channels such as TRPC3, TRPC6, and TRPC7 do not directly interact with STIM1 [32]. However, TRPC3 and TRPC7 contribute to SOC channels when they heteromerize with TRPC1; TRPC1/TRPC3 [45, 119] as well as TRPC1/TRPC3/TRPC7 [127] SOC channels have been described. TRPC4, on the other hand, does not appear to interact with TRPC3, TRPC6, or TRPC7 [31]. It can be suggested that TRPC1, TRPC4, and TRPC2 have the potential to form SOCs (i.e., as they interact with STIM1), and TRPC3 and TRPC7 can form SOC by interacting with TRPC1, as the latter can interact with STIM1 and receive the ER signal. Thus, the regulatory components associated with the individual TRPC proteins determine the type of channel that is formed (see Fig. 1). The exact stoichiometry of TRPC monomers required to generate SOCs is not yet known. It is interesting that TRPC3 and TRPC6 interact with an ER-lumen protein, junctate, which is involved in the ER–PM interaction in muscle cells. Knockdown of junctate cells decreased agonist-induced Ca^{2+} entry as well as SOCE, whereas overexpression of the protein increased ER–PM connections and increased Ca^{2+} entry [111]. Thus, junctate is another ER-calcium-binding protein that appears to mediate ER-PM signaling during activation of SOCE. TRPC1, together with TRPC4, contributes to SOCE and function of dystrophic skeletal muscle fibers [112], while TRPC3 forms SOC channels in cardiac muscle [68]. Whether interaction with junctate confers store-dependent regulation of these TRPCs is not yet known. As it is likely that STIM1 is also present in these cells, the relative roles of STIM1 and junctate in the regulation of SOC channels need to be further investigated.

Based on these findings, it can be suggested that the ER proteins, junctate and STIM1, could fulfill the role of "ER-Ca^{2+} sensor" function proposed in the conformational coupling model. The initial model, which was based on the regulation of voltage-gated calcium channels by the ryanodine receptor in skeletal muscle, suggested IP_3R as

the ER protein involved in activation of SOCE. While there are strong data that IP_3Rs are involved in regulation of SOCE via TRPC channels, the data are somewhat contradictory. As noted above, in many instances, an increase in the association of IP_3R and TRPC channels has been seen during activation of Ca^{2+} entry [36, 52, 57, 90]. However, other studies predict dissociation of TRPC from IP_3R during activation [37, 126]. Despite the lack of clear understanding as to how IP_3R regulates PM membrane TRPC channels, it is important to note that IP_3Rs are seen to be present in all mammalian TRPC channelosomes. CaM, which mediates Ca^{2+}-dependent feedback inhibition of TRPC channels, is also found in almost all TRPC channelosomes, and evidence for direct interaction of CaM with various TRPCs has been reported. Interestingly, IP_3R and CaM have been proposed to have antagonistic effects in the activation of TRPC1, with CaM being inhibitory and IP_3R activating the channel by displacing CaM [131]. Thus, as in the case of *Drosophila* TRP channelosome, the proteins involved in the activation and inactivation of TRPC channels are localized in the TRPC channelosomes where they directly or indirectly interact with the channel proteins. Whether different proteins serve the same function in different cell types is not yet clear, e.g., are the relative roles of junctate and STIM1 as the signal relayers cell-specific?

Targeting and trafficking TRPC channelosomes also contain scaffolding proteins that determine the localization of the channel complex in the cell. Scaffolding proteins, such as RACK1, HOMER, IP_3R, ezrin, caveolin, junctate, ZO1, EBP50, and NHERF (see Table 2), are likely to be involved in retaining TRPC channelosomes in predetermined ER–PM junctional regions as well as mediating interaction of TRPCs with other regulatory proteins to facilitate Ca^{2+} entry-dependent regulation of cell function. TRPC1 is localized in the basolateral region of salivary acinar cells [49, 96], while TRPC3 is found in the apical membrane of ductal cells [5]. TRPC3 + TRPC6 channels are found in the apical region of MDCK cells, while TRPC6 is found in the lateral membranes as well [5]. TRPC4 and TRPC5 are localized in the apical region of polarized cells where they interact with NHERF [105]. The latter is a PDZ domain-containing protein which regulates apical localization of a number of ion transporters. Thus, it is quite likely that in addition to the surface expression, NHERF also determines the apical localization of TRPC4 and TRPC5. Interaction of these channels with ZO1 positions them in the lateral area of endothelial cells where they can control functions like permeability. TRPC5 is found in hippocampal neuronal cells where it is packaged into vesicles together with the growth cone-enriched protein stathmin 2 and carried to newly forming growth cones and synapses [8, 26]. Activation of these homomeric TRPC5 channels by EGF-dependent signaling inhibits growth cone extension. Conversely, TRPC5 + TRPC1 heteromeric channel is excluded from the growth cones, and its activity does not affect the growth of the neurons. It is presently unclear what governs the differential localization of the two TRPC5-containing channels. Most likely, distinct scaffolding proteins are involved in holding the channels at these two different sites. The accessory proteins for TRPCs appear to serve similar functions as those reported for glutamate receptor (GluR), which also interact to form homo- or hetero-tetramers with varying Ca^{2+} selectivities. Although these channels are primarily localized in the post-synaptic membrane, they are regulated and trafficked very differently. While some GluR complexes are constitutively active, others are dynamically regulated. Accessory proteins distinctly control their targeting, clustering, surface expression, and internalization. In addition to PDZ domain-containing proteins such as PICK1, GluRs also interact with four-transmembrane domain-containing proteins, TARPS, which regulate their surface expression and gating. TARPs are similar to the β-subunit of voltage-gated channels which serve a similar function. While β-subunits have not yet been identified for TRPC channels, an emerging theme regarding regulation of their function is their regulated trafficking in response to stimulation of the cell [3, 62, 65]. All TRPCs, other than TRPC2 and TRPC7, have been shown to undergo regulated trafficking and insertion into the PM in response to stimulation of PIP_2 hydrolysis or internal Ca^{2+} store depletion. Consistent with this, a number of proteins that are involved in vesicle trafficking and membrane fusion events have been found to be associated with TRPC proteins. Vesicle-associated SNARE proteins, as well as dynamin, clathrin, PI3K, rac, RhoA, and caveolin-1, have been identified as components of different TRPC channelosomes (see Table 2). Interestingly, EBP50, a scaffolding protein, was shown to affect the gating of TRPC5 channels [70].

The presence of a number of cytoskeletal components as well as actin-interacting proteins in TRPC channelosomes suggests that cytoskeletal remodeling might be involved in the trafficking of TRPC channels to the surface membrane. Regulation of PIP_2 signaling by small G-proteins and their effectors is key to many biological functions. Through selective recruitment and activation of different PIPK isoforms, small G-proteins such as Rho, rac, and Cdc42 modulate actin dynamics and cytoskeleton-dependent cellular events in response to extracellular signaling. These activities affect a number of processes, including endocytosis. It is important to note that localized changes in the cytoskeleton can induce local change in the PM morphology, for example ruffling. Rho-GTPase has been reported to have a role in trafficking of TRPC1. In addition, rac and PI3K have been shown to regulate trafficking of TRPC5.

Although the remodeling of cytoskeleton associated with the activation of TRPC-SOC or TRPC-SMOC channels have not yet been directly assessed, several studies demonstrate that PIP_2 hydrolysis leads to localized cytoskeletal changes [28]. Thus, it can be suggested that such changes might be coordinated with the activation or inactivation of Ca^{2+} entry.

Coordination and compartmentalization of Ca^{2+} signals As discussed above, both PM lipids and proteins are critically involved in the assembly and regulation of TRP channels. While lipids, e.g., PIP_2 can directly regulate activity of a number of TRPC channels, changes in the lipid composition can also elicit effects via cytoskeletal remodeling or regulation of vesicle trafficking. One concept that has gained much attention is that vesicle fusion or channel targeting is not an arbitrary event, but involves precise spatiotemporal resolution. It is well established that lipids are heterogeneously localized within the PM lipid bilayer. As noted above, enrichment of cholesterol, PIP_2, and sphingolipids in certain regions of the PM results in the formation of biochemically distinct lipid raft domains. These domains form the center for the coordinating events associated with cytoskeletal remodeling and PIP_2 metabolism [58]. Further, it is also suggested that vesicle fusion events are concentrated in these regions, as SNARE proteins are enriched in these domains [35, 94]. Cholesterol-binding proteins such as caveolin-1 are found within lipid rafts and act as a scaffold for the assembly of signaling protein complexes. Lipid modification, such as acylation, of proteins as well as their interaction with PIP_2 via PH domains targets their localization into lipid rafts. Thus, it is significant that several TRPCs, TRPC1, TRPC3, TRPC4, and TRPC5, have been reported to be associated with lipid raft domains. It is reasonable to propose that the relatively high concentration of PIP_2 in these regions, presence of scaffolding proteins, as well as proteins involved in PIP_2 metabolism and cytoskeletal remodeling allows targeting, clustering, and regulation of TRPC channels. While it is known that the core components of the TRPC channels, i.e., the TRPC monomers, are assembled in the ER, it is not clear when other accessory components are recruited and how the channel complex is routed to and assembled in the PM. Irrespective of the lack of such data, it is reasonable to suggest that assembly and regulation of TRPC channels within specialized cellular domains facilitates the generation and precise regulation of distinct $[Ca^{2+}]_i$ microdomains. The amplitude and duration of these localized $[Ca^{2+}]_i$ signals will be determined by mechanisms generating the Ca^{2+} signal (Ca^{2+} internal release and entry, channel trafficking and activation, etc.) and those involved in decay of the signal (channel inactivation, Ca^{2+} pumping, diffusion, etc.). In most cases, Ca^{2+}-regulated proteins, such as kinases, phosphatases, vesicle fusion proteins, CaM, etc., are either already scaffolded within the TRPC channelosomes or are recruited into the complex after stimulation so that the changes in $[Ca^{2+}]_i$ can be tightly regulated. Such local $[Ca^{2+}]_i$ changes are likely to be important in the regulation of acute (activation of ion-channels, secretion, etc.) and/or long-term (activation of transcription, proliferation, etc.) cellular functions. An important question that needs to be addressed is how different cell types "custom design" the components, function, and localization of TRPC channelosomes to provide the spatiotemporal Ca^{2+} signals required for regulation of specific physiological function.

Concluding remarks

In conclusion, TRPC channels are activated and regulated within signaling microdomains. Activity of TRPC channels can generate local $[Ca^{2+}]_i$ microdomains or modify the duration and/or amplitude of local $[Ca^{2+}]_i$. This segregated Ca^{2+} signal can be decoded for the regulation of specific downstream functions. Further, recent data suggest that TRPC-channel complexes are remodeled after stimulation, including association with other proteins as well as clustering. Both acute and long-term remodeling have been observed. For example, prolonged stimulation of cells has been shown to alter the expression of TRPC proteins, and in some cases, compensatory changes in other TRPC proteins, which in turn affect the Ca^{2+} entry signal and Ca^{2+}-dependent regulation of cell function. For example, in TRPC6−/− mice, compensatory increase in TRPC3 expression generates spontaneously active channels that induce vascular smooth muscle contraction. Similarly, increases in TRPC1 expression have been associated with anti-apoptotic events in cells. Thus, TRPC channels can be considered to contribute to the "plasticity" of Ca^{2+} homeostasis by modulating, either acutely or long-term, local Ca^{2+} signals and providing a platform for the regulation of specific Ca^{2+}-dependent cellular functions. The ion permeability of specific TRPC channels, as well as their ability to interact with various signaling proteins, is likely to be critical determinants for the generation of these regulatory Ca^{2+} microdomains. While receptor-coupled PIP_2 hydrolysis appears to be a basic process underlying activation of TRPC channels, it is quite likely that they are involved in the regulation of discrete and highly specialized cellular functions which require a customized Ca^{2+} signaling "tool kit" [5]. Future studies directed towards resolving the functional organization of different TRPC channels should take into account the specific downstream function(s) that is regulated.

References

1. Ambudkar IS (2004) Cellular domains that contribute to Ca^{2+} entry events. Sci STKE 243:pe32
2. Ambudkar IS (2006) Ca^{2+} signaling microdomains: platforms for the assembly and regulation of TRPC channels. Trends Pharmacol Sci 27:25–32
3. Ambudkar IS (2007) Trafficking of TRP channels: determinants of channel function. Handb Exp Pharmacol 179:541–557
4. Ambudkar IS (2007) TRPC1: a core component of store-operated calcium channels. Biochem Soc Trans 35:96–100
5. Bandyopadhyay BC, Swaim WD, Liu X, Redman RS, Patterson RL, Ambudkar IS (2005) Apical localization of a functional TRPC3/TRPC6-Ca^{2+}-signaling complex in polarized epithelial cells. Role in apical Ca^{2+} influx. J Biol Chem 280:12908–12916
6. Beech DJ (2005) TRPC1: store-operated channel and more. Pflugers Arch 451:53–60
7. Berridge MJ, Bootman MD, Roderick HL (2003) Calcium signalling: dynamics, homeostasis and remodelling. Nat Rev Mol Cell Biol 4:517–529
8. Bezzerides VJ, Ramsey IS, Kotecha S, Greka A, Clapham DE (2004) Rapid vesicular translocation and insertion of TRP channels. Nat Cell Biol 6:709–720
9. Bollimuntha S, Cornatzer E, Singh BB (2005a) Plasma membrane localization and function of TRPC1 is dependent on its interaction with beta-tubulin in retinal epithelium cells. Vis Neurosci 22:163–170
10. Bollimuntha S, Singh BB, Shavali S, Sharma SK, Ebadi M (2005b) TRPC1-mediated inhibition of 1-methyl-4-phenylpyridinium ion neurotoxicity in human SH-SY5Y neuroblastoma cells. J Biol Chem 280:2132–2140
11. Bolotina VM (2004) Store-operated channels: diversity and activation mechanisms. Sci STKE 2004:pe34
12. Boulay G (2002) Ca(2+)-calmodulin regulates receptor-operated Ca(2+) entry activity of TRPC6 in HEK-293 cells. Cell Calcium 32:201–207
13. Brazer SC, Singh BB, Liu X, Swaim W, Ambudkar IS (2003) Caveolin-1 contributes to assembly of store-operated Ca^{2+} influx channels by regulating plasma membrane localization of TRPC1. J Biol Chem 278:27208–27215
14. Brueggemann LI, Markun DR, Henderson KK, Cribbs LL, Byron KL (2006) Pharmacological and electrophysiological characterization of store-operated currents and capacitative Ca (2+) entry in vascular smooth muscle cells. J Pharmacol Exp Ther 317:488–499
15. Cayouette S, Lussier MP, Mathieu EL, Bousquet SM, Boulay G (2004) Exocytotic insertion of TRPC6 channel into the plasma membrane upon Gq protein-coupled receptor activation. J Biol Chem 279:7241–7246
16. Chu X, Tong Q, Cheung JY, Wozney J, Conrad K, Mazack V, Zhang W, Stahl R, Barber DL, Miller BA (2004) Interaction of TRPC2 and TRPC6 in erythropoietin modulation of calcium influx. J Biol Chem 279:10514–10522
17. Cioffi DL, Wu S, Stevens T (2003) On the endothelial cell ISOC. Cell Calcium 33:323–336
18. Delmas P (2004) Assembly and gating of TRPC channels in signalling microdomains. Novartis Found Symp 258:75–89; discussion 89–102, 263–266
19. Dietrich A, Kalwa H, Rost BR, Gudermann T (2005) The diacylgylcerol-sensitive TRPC3/6/7 subfamily of cation channels: functional characterization and physiological relevance. Pflugers Arch 451:72–80
20. Dietrich A, Mederos YSM, Gollasch M, Gross V, Storch U, Dubrovska G, Obst M, Yildirim E, Salanova B, Kalwa H, Essin K, Pinkenburg O, Luft FC, Gudermann T, Birnbaumer L (2005) Increased vascular smooth muscle contractility in TRPC6−/− mice. Mol Cell Biol 25:6980–6989
21. Downes CP, Gray A, Lucocq JM (2005) Probing phosphoinositide functions in signaling and membrane trafficking. Trends Cell Biol 15:259–268
22. Engelke M, Friedrich O, Budde P, Schafer C, Niemann U, Zitt C, Jungling E, Rocks O, Luckhoff A, Frey J (2002) Structural domains required for channel function of the mouse transient receptor potential protein homologue TRP1beta. FEBS Lett 523:193–199
23. Fiorio Pla A, Maric D, Brazer SC, Giacobini P, Liu X, Chang YH, Ambudkar IS, Barker JL (2005) Canonical transient receptor potential 1 plays a role in basic fibroblast growth factor (bFGF)/FGF receptor-1-induced Ca^{2+} entry and embryonic rat neural stem cell proliferation. J Neurosci 25:2687–2701
24. Freichel M, Suh SH, Pfeifer A, Schweig U, Trost C, Weibgerber P, Biel M, Philipp S, Freise D, Droogmans G, Hofmann F, Flockerzi V, Nilius B (2001) Lack of an endothelial store-operated Ca^{2+} current impairs agonist-dependent vasorelaxation in TRP4−/− mice. Nat Cell Biol 3:121–127
25. Goel M, Sinkins W, Keightley A, Kinter M, Schilling WP (2005) Proteomic analysis of TRPC5- and TRPC6-binding partners reveals interaction with the plasmalemmal Na(+)/K(+)-ATPase. Pflugers Arch 451:87–98
26. Greka A, Navarro B, Oancea E, Duggan A, Clapham DE (2003) TRPC5 is a regulator of hippocampal neurite length and growth cone morphology. Nat Neurosci 6:837–845
27. Henley JM (2003) Proteins interactions implicated in AMPA receptor trafficking: a clear destination and an improving route map. Neurosci Res 45:243–254
28. Hilpela P, Vartiainen MK, Lappalainen P (2004) Regulation of the actin cytoskeleton by PI(4,5)P2 and PI(3,4,5)P3. Curr Top Microbiol Immunol 282:117–163
29. Hisatsune C, Kuroda Y, Nakamura K, Inoue T, Nakamura T, Michikawa T, Mizutani A, Mikoshiba K (2004) Regulation of TRPC6 channel activity by tyrosine phosphorylation. J Biol Chem 279:18887–18894
30. Hisatsune C, Mikoshiba K (2005) Novel compartment implicated in calcium signaling-is it an "induced coupling domain"? Sci STKE 2005:pe53
31. Hofmann T, Schaefer M, Schultz G, Gudermann T (2002) Subunit composition of mammalian transient receptor potential channels in living cells. Proc Natl Acad Sci USA 99:7461–7466
32. Huang GN, Zeng W, Kim JY, Yuan JP, Han L, Muallem S, Worley PF (2006) STIM1 carboxyl-terminus activates native SOC, I(crac) and TRPC1 channels. Nat Cell Biol 8:1003–1010
33. Hui H, McHugh D, Hannan M, Zeng F, Xu SZ, Khan SU, Levenson R, Beech DJ, Weiss JL (2006) Calcium-sensing mechanism in TRPC5 channels contributing to retardation of neurite outgrowth. J Physiol 572:165–172
34. Irvine RF (1990) 'Quantal' Ca^{2+} release and the control of Ca^{2+} entry by inositol phosphates—a possible mechanism. FEBS Lett 263:5–9
35. Isshiki M, Anderson RG (2003) Function of caveolae in Ca^{2+} entry and Ca^{2+}-dependent signal transduction. Traffic 4:717–723
36. Kim JY, Saffen D (2005) Activation of M1 muscarinic acetylcholine receptors stimulates the formation of a multiprotein complex centered on TRPC6 channels. J Biol Chem 280:32035–32047
37. Kim JY, Zeng W, Kiselyov K, Yuan JP, Dehoff MH, Mikoshiba K, Worley PF, Muallem S (2006) Homer 1 mediates store- and inositol 1,4,5-trisphosphate receptor-dependent translocation and retrieval of TRPC3 to the plasma membrane. J Biol Chem 281:32540–32549
38. Kiselyov K, Kim JY, Zeng W, Muallem S (2005) Protein–protein interaction and function: TRPC channels. Pflugers Arch 451:116–124
39. Kiselyov K, Shin DM, Muallem S (2003) Signalling specificity in GPCR-dependent Ca^{2+} signalling. Cell Signal 15:243–253

40. Lepage PK, Lussier MP, Barajas-Martinez H, Bousquet SM, Blanchard AP, Francoeur N, Dumaine R, Boulay G (2006) Identification of two domains involved in the assembly of transient receptor potential canonical channels. J Biol Chem 281:30356–30364
41. Li Q, Luo X, Muallem S (2004) Functional mapping of Ca^{2+} signaling complexes in plasma membrane microdomains of polarized cells. J Biol Chem 279:27837–27840
42. Li Y, Jia YC, Cui K, Li N, Zheng ZY, Wang YZ, Yuan XB (2005) Essential role of TRPC channels in the guidance of nerve growth cones by brain-derived neurotrophic factor. Nature 434:894–898
43. Liman ER, Corey DP, Dulac C (1999) TRP2: a candidate transduction channel for mammalian pheromone sensory signalling. Proc Natl Acad Sci USA 96:5791–5796
44. Liou J, Kim ML, Heo WD, Jones JT, Myers JW, Ferrell JE Jr, Meyer T (2005) STIM is a Ca^{2+} sensor essential for Ca^{2+}-store-depletion-triggered Ca^{2+} influx. Curr Biol 15:1235–1241
45. Liu X, Bandyopadhyay BC, Singh BB, Groschner K, Ambudkar IS (2005) Molecular analysis of a store-operated and 2-acetyl-sn-glycerol-sensitive non-selective cation channel. Heteromeric assembly of TRPC1-TRPC3. J Biol Chem 280:21600–21606
46. Liu X, Groschner K, Ambudkar IS (2004) Distinct Ca(2+)-permeable cation currents are activated by internal Ca(2+)-store depletion in RBL-2H3 cells and human salivary gland cells, HSG and HSY. J Membr Biol 200:93–104
47. Liu X, Rojas E, Ambudkar IS (1998) Regulation of KCa current by store-operated Ca^{2+} influx depends on internal Ca^{2+} release in HSG cells. Am J Physiol 275:C571–C580
48. Liu X, Singh BB, Ambudkar IS (2003) TRPC1 is required for functional store-operated Ca^{2+} channels. Role of acidic amino acid residues in the S5-S6 region. J Biol Chem 278:11337–11343
49. Liu X, Wang W, Singh BB, Lockwich T, Jadlowiec J, O'Connell B, Wellner R, Zhu MX, Ambudkar IS (2000) Trp1, a candidate protein for the store-operated Ca(2+) influx mechanism in salivary gland cells. J Biol Chem 275:3403–3411
50. Lockwich T, Singh BB, Liu X, Ambudkar IS (2001) Stabilization of cortical actin induces internalization of transient receptor potential 3 (Trp3)-associated caveolar Ca^{2+} signaling complex and loss of Ca^{2+} influx without disruption of Trp3-inositol trisphosphate receptor association. J Biol Chem 276:42401–42408
51. Lockwich TP, Liu X, Singh BB, Jadlowiec J, Weiland S, Ambudkar IS (2000) Assembly of Trp1 in a signaling complex associated with caveolin-scaffolding lipid raft domains. J Biol Chem 275:11934–11942
52. Lopez JJ, Salido GM, Pariente JA, Rosado JA (2006) Interaction of STIM1 with endogenously expressed human canonical TRP1 upon depletion of intracellular Ca^{2+} stores. J Biol Chem 281:28254–28264
53. Luik RM, Wu MM, Buchanan J, Lewis RS (2006) The elementary unit of store-operated Ca^{2+} entry: local activation of CRAC channels by STIM1 at ER–plasma membrane junctions. J Cell Biol 174:815–825
54. Lussier MP, Cayouette S, Lepage PK, Bernier CL, Francoeur N, St-Hilaire M, Pinard M, Boulay G (2005) MxA, a member of the dynamin superfamily, interacts with the ankyrin-like repeat domain of TRPC. J Biol Chem 280:19393–19400
55. Ma HT, Venkatachalam K, Li HS, Montell C, Kurosaki T, Patterson RL, Gill DL (2001) Assessment of the role of the inositol 1,4,5-trisphosphate receptor in the activation of transient receptor potential channels and store-operated Ca^{2+} entry channels. J Biol Chem 276:18888–18896
56. Maruyama Y, Nakanishi Y, Walsh EJ, Wilson DP, Welsh DG, Cole WC (2006) Heteromultimeric TRPC6-TRPC7 channels contribute to arginine vasopressin-induced cation current of A7r5 vascular smooth muscle cells. Circ Res 98:1520–1527
57. Mehta D, Ahmmed GU, Paria BC, Holinstat M, Voyno-Yasenetskaya T, Tiruppathi C, Minshall RD, Malik AB (2003) RhoA interaction with inositol 1,4,5-triphosphate receptor and transient receptor potential channel-1 regulates Ca^{2+} entry. J Biol Chem 278:33492–33500
58. Meiri KF (2005) Lipid rafts and regulation of the cytoskeleton during T cell activation. Philos Trans R Soc Lond B Biol Sci 360:1663–1672
59. Menniti FS, Bird GS, Takemura H, Thastrup O, Potter BV, Putney JW Jr (1991) Mobilization of calcium by inositol trisphosphates from permeabilized rat parotid acinar cells. Evidence for translocation of calcium from uptake to release sites within the inositol 1,4,5-trisphosphate- and thapsigargin-sensitive calcium pool. J Biol Chem 266:13646–13653
60. Mertz LM, Baum BJ, Ambudkar IS (1990) Refill status of the agonist-sensitive Ca^{2+} pool regulates Mn^{2+} influx into parotid acini. J Biol Chem 265:15010–15014
61. Mery L, Strauss B, Dufour JF, Krause KH, Hoth M (2002) The PDZ-interacting domain of TRPC4 controls its localization and surface expression in HEK293 cells. J Cell Sci 115:3497–3508
62. Minke H, Cook B (2002) TRP channel proteins and signal transduction. Physiol Rev 82:429–472
63. Mogami H, Tepikin AV, Petersen OH (1998) Termination of cytosolic Ca^{2+} signals: Ca^{2+} reuptake into intracellular stores is regulated by the free Ca^{2+} concentration in the store lumen. EMBO J 17:435–442
64. Mogami H, Nakano K, Tepikin AV, Petersen OH (1997) Ca^{2+} flow via tunnels in polarized cells: recharging of apical Ca^{2+} stores by focal Ca^{2+} entry through basal membrane patch. Cell 88:49–55
65. Montell C (2005) The TRP superfamily of cation channels. Sci STKE 272:re3
66. Mori Y, Wakamori M, Miyakawa T, Hermosura M, Hara Y, Nishida M, Hirose K, Mizushima A, Kurosaki M, Mori E, Gotoh K, Okada T, Fleig A, Penner R, Iino M, Kurosaki T (2002) Transient receptor potential 1 regulates capacitative Ca(2+) entry and Ca(2+) release from endoplasmic reticulum in B lymphocytes. J Exp Med 195:673–681
67. Nagamine K, Kudoh J, Minoshima S, Kawasaki K, Asakawa S, Ito F, Shimizu N (1998) Molecular cloning of a novel putative Ca^{2+} channel protein (TRPC7) highly expressed in brain. Genomics 54:124–131
68. Nakayama H, Wilkin BJ, Bodi I, Molkentin JD (2006) Calcineurin-dependent cardiomyopathy is activated by TRPC in the adult mouse heart. FASEB J 20:1660–1670
69. Nicoll RA, Tomita S, Bredt DS (2006) Auxiliary subunits assist AMPA-type glutamate receptors. Science 311:1253–1256
70. Obukhov AG, Nowycky MC (2004) TRPC5 activation kinetics are modulated by the scaffolding protein ezrin/radixin/moesin-binding phosphoprotein-50 (EBP50). J Cell Physiol 201:227–235
71. Odell AF, Scott JL, Van Helden DF (2005) Epidermal growth factor induces tyrosine phosphorylation, membrane insertion, and activation of transient receptor potential channel 4. J Biol Chem 280:37974–37987
72. Ong HL, Cheng KT, Liu X, Bandyopadhyay BC, Paria BC, Soboloff J, Pani B, Gwack Y, Srikanth S, Singh BB, Gill D, Ambudkar IS (2007) Dynamic assembly of TRPC1/STIM1/Orai1 ternary complex is involved in store-operated calcium influx: evidence for similarities in SOC and CRAC channel components. J Biol Chem 282(12):9105–9116
73. Ong HL, Liu X, Tsaneva-Atanasova K, Singh BB, Bandyopadhyay BC, Swaim WD, Russell JT, Hegde RS, Sherman A, Ambudkar IS (2007) Relocalization of STIM1 for activation of store-operated Ca^{2+} entry is determined by the depletion of subplasma membrane endoplasmic reticulum Ca^{2+} store. J Biol Chem (in press) DOI 10.1074/jbc.M609435200
74. Ordaz B, Tang J, Xiao R, Salgado A, Sampieri A, Zhu MX, Vaca L (2005) Calmodulin and calcium interplay in the modulation of TRPC5 channel activity. Identification of a novel C-terminal

domain for calcium/calmodulin-mediated facilitation. J Biol Chem 280:30788–30796
75. Parekh AB (2003) Store-operated Ca^{2+} entry: dynamic interplay between endoplasmic reticulum, mitochondria and plasma membrane. J Physiol 547:333–348
76. Parekh AB, Putney JW Jr (2005) Store-operated calcium channels. Physiol Rev 85:757–810
77. Patterson RL, Boehning D, Snyder SH (2004) Inositol 1,4,5-trisphosphate receptors as signal integrators. Ann Rev Biochem 73:437–465
78. Patterson RL, van Rossum DB, Gill DL (1999) Store-operated Ca^{2+} entry: evidence for a secretion-like coupling model. Cell 98:487–499
79. Patterson RL, van Rossum DB, Nikolaidis N, Gill DL, Snyder SH (2005) Phospholipase C-gamma: diverse roles in receptor-mediated calcium signaling. Trends Biochem Sci 30:688–697
80. Plant TD, Schaefer M (2005) Receptor-operated cation channels formed by TRPC4 and TRPC5. Naunyn Schmiedebergs Arch Pharmacol 371:266–276
81. Prakriya M, Feske S, Gwack Y, Srikanth S, Rao A, Hogan PG (2006) Orai1 is an essential pore subunit of the CRAC channel. Nature 443:230–233
82. Putney JW Jr (1986) A model for receptor regulated calcium entry. Cell Calcium 7:1–12
83. Putney JW (2005) Physiological mechanisms of TRPC activation. Pflugers Arch 451:29–34
84. Putney JW Jr (1990) Capacitative calcium entry revisited. Cell Calcium 11:611–624
85. Putney JW Jr, Broad LM, Braun FJ, Lievremont JP, Bird GS (2001) Mechanisms of capacitative calcium entry. J Cell Sci 114:2223–2229
86. Randriamampita C, Tsien RY (1993) Emptying of intracellular Ca^{2+} stores releases a novel small messenger that stimulates Ca^{2+} influx. Nature 364:809–814
87. Rao JN, Platoshyn O, Golovina VA, Liu L, Zou T, Marasa BS, Turner DJ, Yuan JX, Wang JY (2006) TRPC1 functions as a store-operated Ca^{2+} channel in intestinal epithelial cells and regulates early mucosal restitution after wounding. Am J Physiol Gastrointest Liver Physiol 290:G782–G792
88. Roos J, DiGregorio PJ, Yeromin AV, Ohlsen K, Lioudyno M, Zhang S, Safrina O, Kozak JA, Wagner SL, Cahalan MD, Velicelebi G, Stauderman KA (2005) STIM1, an essential and conserved component of store-operated Ca^{2+} channel function. J Cell Biol 16:435–445
89. Rosado JA, Sage SO (2000) A role for the actin cytoskeleton in the initiation and maintenance of store-mediated calcium entry in human platelets. Trends Cardiovasc Med 10:327–332
90. Rosado JA, Redondo PC, Sage SO, Pariente JA, Salido GM (2005) Store-operated Ca^{2+} entry: vesicle fusion or reversible trafficking and de novo conformational coupling? J Cell Physiol 205:262–269
91. Rychkov G, Barritt GJ (2007) TRPC1 Ca^{2+} permeable channels in animal cells. Handb Exp Pharmacol 179:23–52
92. Schaefer M (2005) Homo- and heteromeric assembly of TRP channel subunits. Pflugers Arch 451:35–42
93. Shimizu S, Yoshida T, Wakamori M, Ishii M, Okada T, Takahashi M, Seto M, Sakurada K, Kiuchi Y, Mori Y (2006) Ca^{2+}-calmodulin-dependent myosin light chain kinase is essential for activation of TRPC5 channels expressed in HEK293 cells. J Physiol 570:219–235
94. Simons K, Toomre D (2000) Lipid rafts and signal transduction. Nat Rev Mol Cell Biol 1:31–39
95. Singh BB, Lockwich TP, Bandyopadhyay BC, Liu X, Bollimuntha S, Brazer SC, Combs C, Das S, Leenders AG, Sheng ZH, Knepper MA, Ambudkar SV, Ambudkar IS (2004) VAMP2-dependent exocytosis regulates plasma membrane insertion of TRPC3 channels and contributes to agonist-stimulated Ca^{2+} influx. Mol Cell 15:635–646
96. Singh BB, Zheng C, Liu X, Lockwich T, Liao D, Zhu MX, Birnbaumer L, Ambudkar IS (2001) Trp1-dependent enhancement of salivary gland fluid secretion: role of store-operated calcium entry. FASEB J 15:1652–1654
97. Smyth JT, Dehaven WI, Jones BF, Mercer JC, Trebak M, Vazquez G, Putney JW Jr (2006) Emerging perspectives in store-operated Ca(2+) entry: roles of Orai, Stim and TRP. Biochim Biophys Acta 1763:1147–1160
98. Spassova MA, Soboloff J, He LP, Hewavitharana T, Xu W, Venkatachalam K, van Rossum DB, Patterson RL, Gill DL (2004) Calcium entry mediated by SOCs and TRP channels: variations and enigma. Biochim Biophys Acta 1742:9–20
99. Stamboulian S, Moutin MJ, Treves S, Pochon N, Grunwald D, Zorzato F, De Waard M, Ronjat M, Arnoult C (2005) Junctate, an inositol 1,4,5-triphosphate receptor associated protein, is present in rodent sperm and binds TRPC2 and TRPC5 but not TRPC1 channels. Dev Biol 286:326–337
100. Strubing C, Krapivinsky G, Krapivinsky L, Clapham DE (2001) TRPC1 and TRPC5 form a novel cation channels in mammalian brain. Neuron 29:645–655
101. Strubing C, Krapivinsky G, Krapivinsky L, Clapham DE (2003) Formation of novel TRPC channels by complex subunit interactions in embryonic brain. J Biol Chem 278:39014–39019
102. Sutton KA, Jungnickel MK, Wang Y, Cullen K, Lambert S, Florman HM (2004) Enkurin is a novel calmodulin and TRPC channel binding protein in sperm. Dev Biol 274:426–435
103. Takemura H, Putney JW (1989) Capacititative calcium entry in parotid acinar cells. Biochem J 258:409–412
104. Tang J, Lin Y, Zhang Z, Tikunova S, Birnbaumer L, Zhu MX (2001) Identification of common binding sites for calmodulin and IP3 receptors on the carboxyl-termini of TRP channels. J Biol Chem 276:21303–21310
105. Tang Y, Tang J, Chen Z, Trost C, Flockerzi V, Li M, Ramesh V, Zhu MX (2000) Association of mammalian Trp4 and phospholipase C isozymes with a PDZ domain-containing protein, NHERF. J Biol Chem 275:27559–27564
106. Thebault S, Flourakis M, Vanoverberghe K, Vandermoere F, Roudbaraki M, Lehen'kyi V, Slomianny C, Beck B, Mariot P, Bonnal JL, Mauroy B, Shuba Y, Capiod T, Skryma R, Prevarskaya N (2006) Differential role of transient receptor potential channels in Ca^{2+} entry and proliferation of prostate cancer epithelial cells. Cancer Res 66:2038–2047
107. Thebault S, Zholos A, Enfissi A, Slomianny C, Dewailly E, Roudbaraki M, Parys J, Prevarskaya N (2005) Receptor-operated Ca^{2+} entry mediated by TRPC3/TRPC6 proteins in rat prostate smooth muscle (PS1) cell line. J Cell Physiol 204:320–328
108. Tiruppathi C, Freichel M, Vogel SM, Paria BC, Mehta D, Flockerzi V, Malik AB (2002) Impairment of store-operated Ca^{2+} entry in TRPC4(−/−) mice interferes with increase in lung microvascular permeability. Circ Res 91:70–76
109. Tong Q, Chu X, Cheung JY, Conrad K, Stahl R, Barber DL, Mignery G, Miller BA (2004) Erythropoietin-modulated calcium influx through TRPC2 is mediated by phospholipase Cgamma and IP3R. Am J Physiol Cell Physiol 287:C1667–C1678
110. Torihashi S, Fujimoto T, Trost C, Nakayama S (2002) Calcium oscillation linked to pacemaking of interstitial cells of Cajal: requirement of calcium influx and localization of TRP4 in caveolae. J Biol Chem 277:19191–19197
111. Treves S, Franzini-Armstrong C, Moccagatta L, Arnoult C, Grasso C, Schrum A, Ducreux S, Zhu MX, Mikoshiba K, Girard T, Smida-Rezgui S, Ronjat M, Zorzato F (2004) Junctate is a key element in calcium entry induced by activation of InsP3 receptors and/or calcium store depletion. J Cell Biol 166:537–548

112. Vandebrouck C, Martin D, Colson-Van Schoor M, Debaix H, Gailly P (2002) Involvement of TRPC in the abnormal calcium influx observed in dystrophic (mdx) mouse skeletal muscle fibers. J Cell Biol 158:1089–1096
113. Vazquez G, Wedel BJ, Bird GS, Joseph SK, Putney JW (2002) An inositol 1,4,5-trisphosphate receptor-dependent cation entry pathway in DT40 B lymphocytes. EMBO J 21:4531–4538
114. Vazquez G, Wedel BJ, Trebak M, St John Bird G, Putney JW Jr (2003) Expression level of the canonical transient receptor potential 3 (TRPC3) channel determines its mechanism of activation. J Biol Chem 278:21649–21654
115. Venkatachalam K, van Rossum DB, Patterson RL, Ma HT, Gill DL (2002) The cellular and molecular basis of store-operated calcium entry. Nat Cell Biol 4:E263–E272
116. Vig M, Beck A, Billingsley JM, Lis A, Parvez S, Peinelt C, Koomoa DL, Soboloff J, Gill DL, Fleig A, Kinet JP, Penner R (2006) CRACM1 multimers form the ion-selective pore of the CRAC channel. Curr Biol 16:2073–2079
117. Villereal ML (2006) Mechanism and functional significance of TRPC channel multimerization. Semin Cell Dev Biol 17: 618–629
118. Wedel BJ, Vazquez G, McKay RR, Bird GSJ, Putney JW Jr (2003) A calmodulin/inositol 1,4,5-trisphosphate (IP3) receptor-binding region targets TRPC3 to the plasma membrane in a calmodulin/IP3 receptor-independent process. J Biol Chem 278:25758–25765
119. Wu X, Zagranichnaya TK, Gurda GT, Eves EM, Villereal ML (2004) A TRPC1/TRPC3-mediated increase in store-operated calcium entry is required for differentiation of H19-7 hippocampal neuronal cells. J Biol Chem 279:43392–43402
120. Xu SZ, Boulay G, Flemming R, Beech DJ (2006) E3-targeted anti-TRPC5 antibody inhibits store-operated calcium entry in freshly isolated pial arterioles. Am J Physiol Heart Circ Physiol 291:H2653–H2659
121. Xu SZ, Muraki K, Zeng F, Li J, Sukumar P, Shah S, Dedman AM, Flemming PK, McHugh D, Naylor J, Cheong A, Bateson AN, Munsch CM, Porter KE, Beech DJ (2006) A sphingosine-1-phosphate-activated calcium channel controlling vascular smooth muscle cell motility. Circ Res 98:1381–1389
122. Yang H, Mergler S, Sun X, Wang Z, Lu L, Bonanno JA, Pleyer U, Reinach PS (2005) TRPC4 knockdown suppresses epidermal growth factor-induced store-operated channel activation and growth in human corneal epithelial cells. J Biol Chem 280:32230–32237
123. Yeromin AV, Zhang SL, Jiang W, Yu Y, Safrina O, Cahalan MD (2006) Molecular identification of the CRAC channel by altered ion selectivity in a mutant of Orai. Nature 443:226–229
124. Yildirim E, Dietrich A, Birnbaumer L (2003) The mouse C-type transient receptor potential 2 (TRPC2) channel: alternative splicing and calmodulin binding to its N terminus. Proc Natl Acad Sci U S A 100:2220–2225
125. Yoon IS, Li PP, Siu KP, Kennedy JL, Macciardi F, Cooke RG, Parikh SV, Warsh JJ (2001) Altered TRPC7 gene expression in bipolar-I disorder. Biol Psychiatry 50:620–626
126. Yuan JP, Kiselyov K, Shin DM, Chen J, Shcheynikov N, Kang SH, Dehoff MH, Schwarz MK, Seeburg PH, Muallem S, Worley PF (2003) Homer binds TRPC family channels and is required for gating of TRPC1 by IP3 receptors. Cell 114:777–789
127. Zagranichnaya TK, Wu X, Villereal ML (2005) Endogenous TRPC1, TRPC3, and TRPC7 proteins combine to form native store-operated channels in HEK-293 cells. J Biol Chem 280:29559–29569
128. Zeng F, Xu SZ, Jackson PK, McHugh D, Kumar B, Fountain SJ, Beech DJ (2004) Human TRPC5 channel activated by a multiplicity of signals in a single cell. J Physiol 559:739–750
129. Zhang SL, Yu Y, Roos J, Kozak JA, Deerinck TJ, Ellisman MH, Stauderman KA, Cahalan MD (2005) STIM1 is a Ca^{2+} sensor that activates CRAC channels and migrates from the Ca^{2+} store to the plasma membrane. Nature 437:902–905
130. Zhu MH, Chae M, Kim HJ, Lee YM, Kim MJ, Jin NG, Yang DK, So I, Kim KW (2005) Desensitization of canonical transient receptor potential channel 5 by protein kinase C. Am J Physiol Cell Physiol 289:C591–C600
131. Zhu MX, Tang J (2004) TRPC channel interactions with calmodulin and IP3 receptors. Novartis Found Symp 258:44–58; discussion 58–62, 98–102, 263–6
132. Zufall F (2005) The TRPC2 ion channel and pheromone sensing in the accessory olfactory system. Naunyn Schmiedebergs Arch Pharmacol 371:245–250