Physiological Functions and Regulation of TRPC Channels

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Contents

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Abstract

The TRP-canonical (TRPC) subfamily, which consists of seven members (TRPC1–TRPC7), are Ca^{2+}-permeable cation channels that are activated in response to receptor-mediated PIP_2 hydrolysis via store-dependent and store-independent mechanisms. These channels are involved in a variety of physiological functions in different cell types and tissues. Of these, TRPC6 has been linked to a channelopathy resulting in human disease. Two key players of the store-dependent regulatory pathway, STIM1 and Orai1, interact with some TRPC channels to gate and regulate channel activity. The Ca^{2+} influx mediated by TRPC channels generates distinct intracellular Ca^{2+} signals that regulate downstream signaling events and consequent cell functions. This requires localization of TRPC channels in specific plasma membrane microdomains and precise regulation of channel function which is coordinated by various scaffolding, trafficking, and regulatory proteins.

Keywords

TRPC channels • Ca^{2+} signaling • Protein complex • Trafficking • Regulation • Function

1 Introduction

TRPC channels were first identified as molecular components of the store-operated calcium entry (SOCE) channels (Ambudkar et al. 2007; Parekh and Putney 2005; Venkatachalam and Montell 2007). SOCE is an ubiquitous Ca^{2+} entry mechanism that is activated in response to stimulation of plasma membrane receptors coupled to phosphatidylinositol 4,5-bisphosphate (PIP_2) hydrolysis, inositol 1,4,5-triphosphate (IP_3) generation, and IP_3 receptor (IP_3R)-mediated Ca^{2+} release from the endoplasmic reticulum (ER). The primary trigger for activation of SOCE is depletion of the ER-Ca^{2+} store, while refilling of this store leads to inactivation. The first store-operated Ca^{2+} current to be identified (I_{CRAC}) was the inwardly rectifying and highly Ca^{2+}-selective current that was measured in mast cells and T lymphocytes (Hoth et al. 1993; Hoth and Penner 1992; Parekh and Penner 1997). The channel mediating this current was termed calcium release-activated calcium (CRAC) channel. Later studies revealed currents with varying electrophysiological characteristics in other cell types (Liu et al. 2004; Parekh and Putney 2005). TRPC channels were proposed as possible molecular components of such channels and indeed, several TRPC members have been reported to contribute to SOCE, although data for some TRPCs are not very consistent. TRPC1 was the first mammalian TRPC channel to be cloned (Wes et al. 1995; Zhu et al. 1995), and early studies established that when activated by conditions resulting in store depletion, it is required for the generation of a relatively Ca^{2+}-selective cation current that was termed I_{SOC} (store-operated Ca^{2+} current; Liu et al. 2003) to

distinguish it from I_{CRAC}. TRPC1 has been most consistently demonstrated to contribute to SOCE in a variety of cell types (Ambudkar et al. 2007; Beech 2005), although heterologous expression of the channel does not always result in consistent functions.

The critical mechanism that senses the status of ER-[Ca^{2+}] and regulates activation of plasma membrane channels mediating SOCE remained a challenge for more than two decades. This component has now been elucidated, with the discovery of STIM1 as the ER Ca^{2+}-sensor protein involved in regulating the plasma membrane channels. Further, Orai1 has been established as the pore-mediating component of CRAC channels. Of further interest is the finding that activation of TRPC channels following store depletion is dependent not only on STIM1 but also on Orai1 (discussed in detail below). The exact mechanism(s) that regulate TRPC channels in the non-store-operated mode is not yet clearly elucidated, although diacylglycerol (DAG), a product of PIP_2 hydrolysis, has been suggested as an endogenous ligand.

2 Physiological Functions of TRPC Channels

The physiological functions ascribed to TRPCs have been determined in cell cultures and animal models. Some human diseases are also associated with loss or gain of channel function. In cell lines and primary cell cultures, endogenous TRPC channel function has been assessed by decreasing protein expression using shRNA or siRNA (Table 1). TRPC1-mediated Ca^{2+} entry regulates endogenous glioma Cl^- channels to facilitate cell migration by promoting cell shape and volume changes (Cuddapah et al. 2013). The channel is also vital for maintaining permeability of endothelial cell barrier, promoting wound healing following injury to the intestinal epithelial layer and protection against cell cytotoxicity (Bollimuntha et al. 2005b; Paria et al. 2004). Other physiological functions that have been attributed to TRPC1 include cell proliferation and synaptic plasticity (Fiorio Pla et al. 2005; Li et al. 2012a; McGurk et al. 2011). Knocking down endogenous TRPC2 levels or expression of a dominant-negative isoform of TRPC2 in rat thyroid FRTL-5 cells severely impacted cell proliferation and migration, as well as cellular adhesion (Sukumaran et al. 2013). TRPC2 and anoctamin 1 have been proposed to function synergistically to modulate iodide transport in thyroid cells (Viitanen et al. 2013). TRPC3 is involved in proliferation and differentiation of various cell types, such as myoblasts, cardiac fibroblasts, and primary T cells (Harada et al. 2012; Wenning et al. 2011; Woo et al. 2010). In some cells, more than one TRPC channels have been shown to regulate the same physiological event. For example, TRPC3, TRPC4, and TRPC5 facilitate in vitro endothelial tube formation by promoting proliferation of endothelial cells (Antigny et al. 2012). TRPC5 and TRPC6 regulate migration of fibroblasts and kidney podocytes in an antagonistic manner, whereby TRPC5 activates Rac1 to promote motility but TRPC6 activates RhoA to inhibit motility (Tian et al. 2010). TRPC5 also plays an important role in facilitating migration of vascular smooth muscle cells, as well as regulating neurite

Table 1 Cell-based assays used to delineate physiological functions of TRPC1–7 channels

TRPC	Physiological function	Protein manipulation	Cell type	References
1	Cell migration	Knockdown	Human malignant gliomas	Cuddapah et al. (2013)
		Overexpression, knockdown	Intestinal epithelial cells	Bomben et al. (2011), Rao et al. (2006)
	Cell proliferation	Knockdown	Neural stem, hippocampal neural progenitor cells	Fiorio Pla et al. (2005), Li et al. (2012a), McGurk et al. (2011)
	Synaptic plasticity	Knockdown	Neuromuscular junctions	McGurk et al. (2011)
2	Cell proliferation, migration	Knockdown, dominant negative	Rat thyroid cells	Sukumaran et al. (2013)
	Iodide transport	Knockdown	Rat thyroid cells	Viitanen et al. (2013)
3	Cell proliferation	Knockdown	Muscular dysgenic myoblasts, cardiac fibroblasts, endothelial cells, pontine neurons, primary T cells	Antigny et al. (2012), Harada et al. (2012), Li et al. (2005), Wenning et al. (2011), Woo et al. (2010)
	Cell differentiation	Knockdown	Muscular dysgenic myoblasts, cardiac fibroblasts	Harada et al. (2012), Woo et al. (2010)
4	Cell proliferation	Knockdown	Endothelial cells	Antigny et al. (2012)
5	Cell migration	Knockdown	Fibroblasts, kidney podocytes	Tian et al. (2010)
		Antibody block	Vascular smooth muscle cells	Greka et al. (2003), Tian et al. (2010), Xu et al. (2006)
	Cell proliferation	Knockdown	Endothelial cells	Antigny et al. (2012)
	Neurite extension, growth cone morphology	Dominant-negative, interacting protein knockdown	Hippocampal neurons	Greka et al. (2003), Tian et al. (2010), Xu et al. (2006)
6	Cell migration	Knockdown	Fibroblasts, kidney podocytes	Tian et al. (2010)
	Cell proliferation	Knockdown	Pontine neurons, prostate cancer epithelial cells	Li et al. (2005), Thebault et al. (2006)

extension and growth cone morphology of hippocampal neurons (Greka et al. 2003; Tian et al. 2010; Xu et al. 2006). TRPC6 regulates the growth of pontine neurons (in addition to TRPC3) (Li et al. 2005) and prostate cancer epithelial cells (Thebault et al. 2006).

The physiological functions of TRPC channels has been revealed by studies using knockout mouse models (discussed in further detail in Chapters 2 to 8 of volume 1,

"TRPC1", "TRPC2", "TRPC3: A Multifunctional Signaling Molecule", "TRPC4- and TRPC4-Containing Channels"; "TRPC5", "TRPC6: Physiological Function and Pathophysiological Relevance" and "Transient Receptor Potential Canonical 7: A Diacylglycerol-Activated Non-selective Cation Channel"). In addition to knockout mouse models, mice expressing dominant-negative isoforms of TRPC3, TRPC4, and TRPC6 reveal that these channels are involved in the development of cardiac hypertrophy via a calcineurin-NFAT signaling pathway (Wu et al. 2010). Various dominant-negative isoforms of TRPCs have been generated, e.g., pore-dead channel created by mutations in the pore region. Others, such as the TRPC3 N-terminus (amino acids 1–302), also exert dominant-negative effects when overexpressed by disrupting channel assembly since TRPCs interact via their N-terminal regions (Balzer et al. 1999). In the case of TRPC4, an N-terminal fragment that includes the first ankyrin-like repeat has been used (Schindl et al. 2008). In other studies, TRPC function has been revealed by using disease models. A mouse model for Parkinson's disease (PD) shows the vital role of TRPC1 in maintaining calcium homeostasis, promoting neuronal survival to limit neuronal degeneration, and possibly slowing down or preventing the onset of progression of PD. PD-associated symptoms are ameliorated by heterologous expression of TRPC1 in neuronal cells or in vivo intranigral injection of TRPC1-containing adenovirus particles in PD mouse model (Selvaraj et al. 2009, 2012).

A number of other mouse models also reveal important information regarding TRPC channel regulation. Physiological functions attributed to TRPC1 are severely affected in caveolin-deficient (Cav-1$^{-/-}$) and Homer1-deficient (Homer1$^{-/-}$) mice. Knocking out caveolin-1 (Cav-1) results in mislocalization of TRPC1 due to aberrant trafficking, leading to impaired channel function that significantly reduces salivary gland fluid secretion (Pani et al. 2012). Loss of Homer1, a scaffolding protein that mediates TRPC1 interaction with the IP_3R, causes aberrant calcium signaling resulting in skeletal myopathy (Stiber et al. 2008). The *Mecp2* mutant mice are a model system for Rett syndrome, which is caused by loss-of-function mutations in the *Mecp2* gene. These mice display sensory and motor abnormalities due to loss of TRPC3 function in hippocampal neurons, although potential contributions from TRPC6 or TRPC7 have not been ruled out (Li et al. 2012b). Interestingly, in some studies, an increase of TRPC expression and function has been proposed to underlie disease onset and/or progression. Studies with Duchenne muscular dystrophy (*mdx*) mice demonstrate an increase in TRPC1-mediated Ca^{2+} influx induces muscle damage (Gervasio et al. 2008; Williams and Allen 2007). Expression of TRPC1, TRPC5, and TRPC6 is significantly elevated in adrenal medulla of Ossabaw miniature pigs are used to study the metabolic syndrome or pre-diabetes state (Hu et al. 2009). Perturbations in Ca^{2+} signaling and homeostasis have been correlated with increased TRPC3 expression and function in cardiomyocytes obtained from muscle LIM protein knockout mice (model for the myocardial disorder, dilated cardiomyopathy) (Kitajima et al. 2011) and spontaneously hypertensive rats (model for hypertension) (Adebiyi et al. 2012; Bush et al. 2006; Noorani et al. 2011). TRPC7 has been implicated in myocardial apoptosis failure as its expression is upregulated in Dahl salt-sensitive rats with heart failure and has been proposed to be a novel target for treatment of heart failure (Satoh et al. 2007).

The genes encoding TRPC channels have also been linked to various human diseases, such as cardiovascular, pulmonary, and neurological, as well as cancer (Nilius and Owsianik 2010). For example, *trpc5* and *trpc6* loci are linked with infantile hypertrophic pyloric stenosis, a very common condition of stomach obstruction that is characterized by projectile vomiting. Increased *trpc6* promoter activity and TRPC6 expression have been linked to the development of idiopathic pulmonary arterial hypertension, which is caused by excessive proliferation of pulmonary artery smooth muscle cells. Nonetheless, the only TRPC-related channelopathy reported so far is focal and segmental glomerulosclerosis (FSGS), which is linked to a mutation of the *trpc6* gene. These mutations resulted in alterations of residues in the N- and C-termini, leading to significantly elevated TRPC6-mediated calcium signaling that may affect channel interaction with podocyte structural proteins, leading to defects in the filtration barrier. Alternatively, the elevated calcium signaling mediated via TRPC6 may lead to apoptosis, resulting in a defective permeability barrier (Mukerji et al. 2007; Nilius and Owsianik 2010). Nonetheless, some TRPC6 variants linked to FSGS have also been reported to not cause any change in channel activity (Reiser et al. 2005).

3 TRPC Channel Complexes

Much of the initial insights into TRPC protein interactions are based on studies with the *Drosophila* TRP channel which is localized in the *Drosophila* eye and plays a critical role in phototransduction (Venkatachalam and Montell 2007). This TRP channel resides in a multiprotein signalplex with proteins that are important for proper channel assembly, retention, activity, regulation of phototransduction, and downstream signaling. The scaffolding protein INAD forms the core of this complex since it has the ability, via multiple PDZ domains, to bind to numerous signaling proteins and serve as a platform for their interaction with TRP and regulation of channel function (Venkatachalam and Montell 2007). Critical amino acid sequences that are conserved in TRP channel families appear to be involved in these various, but specific, protein–protein interactions. These include the coiled-coiled domain, ankyrin repeat region, calmodulin- and lipid-binding domains, as well as other less well-characterized protein binding domains. Since mammalian TRPC proteins share many of the same structural components as the *Drosophila* TRP channel, it has been hypothesized that the individual TRPC protein is also capable of forming homomeric or heteromeric interactions with other TRPC channels and signaling proteins. It is now well established that a number of key signaling and scaffolding proteins are associated with mammalian TRPC channels (Ambudkar et al. 2006; Ambudkar and Ong 2007; Kiselyov et al. 2007).

3.1 TRPC1

TRPC1 interacts with other TRPCs to form channels with diverse properties, ranging from relatively Ca^{2+}-selective to non-selective (Ca^{2+} vs. Na^{+}) (Cheng

et al. 2013). In human submandibular gland (HSG) cells, TRPC1 contributes to a relatively Ca^{2+}-selective cation channel, possibly via a homomeric TRPC channel (Liu et al. 2004). Several TRPCs are endogenously expressed in cells, for example, TRPC1 and TRPC3 in HEK293 cells and neuronal cells (Zhu et al. 1995, 1996). Based on the association of TRPC1 and TRPC3 in heterologous expression systems, it can be suggested that the endogenous channels can also assemble in heteromeric complexes. Indeed, endogenous heteromeric TRPC channels have been described in different cell types: e.g., TRPC1 + TRPC3 in HSY cells (Liu et al. 2005), TRPC1 + TRPC3 + TRPC7 in HEK293 cells (Zagranichnaya et al. 2005), TRPC1 + TRPC4 in mesangial cells (Sours-Brothers et al. 2009) and endothelial cells (Sundivakkam et al. 2012), and TRPC1 + TRPC5 in neuronal cells, vascular endothelial cells, and vascular smooth muscle cells (Goel et al. 2002; Shi et al. 2012; Strubing et al. 2001; Xu et al. 2006). TRPC1 forms a macromolecular complex with TRPC6, SERCA, and IP_3R following passive depletion of the ER-Ca^{2+} stores in human platelets (Redondo et al. 2008).

TRPC1 also interacts with non-TRPC channels, such as Orai1 (Cheng et al. 2008; Lu et al. 2010), TRPV4 (Ma et al. 2010, 2011), and TRPV6 (Schindl et al. 2012). The association with Orai1 is a critical determinant of TRPC1 function (further discussed below). Although it is unclear whether there is a physical interaction between the two channels, studies have clearly established that Orai1 and TRPC1 form distinct STIM1-gated channels in the membrane that are activated following store depletion (Cheng et al. 2008; Lu et al. 2010). In a recent study, a splice variant of TRPC1 has been shown to regulate the activity of Orai1 (Ong et al. 2013). TRPC1 + TRPV4 forms a heteromeric channel involved in SOCE in vascular smooth muscle cells as well as endothelial cells (Ma et al. 2010, 2011). TRPC1 can also interact with and negatively regulate TRPV6 channel activity, without generation of a heteromeric channel, in HEK293 cells (Schindl et al. 2012).

In addition to calcium channels, TRPC1 interacts with a wide range of signaling proteins, as well as scaffolding and trafficking proteins (Table 2). The TRPC1 signaling complex contains key Ca^{2+} signaling proteins that function upstream in the agonist-activated signaling cascade, such as PLC, CaM, $G_{q/11}$, IP_3R, PMCA, SERCA, and STIM1 (Cheng et al. 2008; Heo et al. 2012; Huang et al. 2006; Lockwich et al. 2000; Lu et al. 2010; Ng et al. 2009; Ong et al. 2007; Pani et al. 2009; Redondo et al. 2008; Selvaraj et al. 2012 ; Singh et al. 2002; Sundivakkam et al. 2009; Tang et al. 2001; Yuan et al. 2003). Such findings have led to the proposal that TRPC1 channel complexes are composed of proteins from both ER and plasma membranes and likely represent cellular microdomains where these two membranes are in close proximity to each other. The interaction with STIM1 is critically required for channel activation following store depletion. Additionally, TRPC1 activity is also regulated via its binding to IP_3R as it has the CaM-/IP_3R-binding (CIRB) domain in the C-terminus. Both CaM and IP_3R bind competitively to TRPC1 to modulate channel activity, with IP_3R involved in channel activation and CaM regulating the Ca^{2+}-dependent feedback inhibition (Singh et al. 2002; Tang et al. 2001). It is interesting that the STIM1- and IP_3R-binding domains lie in close proximity in the C-terminus of TRPC1. However, it is yet unclear whether STIM1 and the IP_3R are simultaneously involved in activation

Table 2 Interacting partners for TRPC1–7 channels

Channel	Other channels	Signaling proteins	Scaffolding and trafficking proteins
TRPC1	TRPC1[a] TRPC3 (Xu et al. 1997) TRPC4, TRPC5 (Strubing et al. 2001) TRPC6 (Strubing et al. 2003) TRPC7 (Zagranichnaya et al. 2005) TRPV4 (Ma et al. 2010) TRPV6 (Schindl et al. 2012) Orai1 (Cheng et al. 2008)	IP_3R, CaM, $G_{q/11}$ (Lockwich et al. 2000) PLCγ (Tu et al. 2005) PMCA (Singh et al. 2002) SERCA (Redondo et al. 2008) STIM1 (Huang et al. 2006)	β-tubulin (Bollimuntha et al. 2005a) Cav-1 (Lockwich et al. 2000) Enkurin (Sutton et al. 2004) Homer (Yuan et al. 2003) MxA (Lussier et al. 2005) RhoA (Mehta et al. 2003) SNAP-25, VAMP (Redondo et al. 2004)
TRPC2	TRPC6 (Chu et al. 2004; Tong et al. 2004)	CaM (Tang et al. 2001) epoR, IP_3R, PLCγ (Chu et al. 2004; Tong et al. 2004) STIM1 (Huang et al. 2006)	Enkurin (Sutton et al. 2004) Homer1 (Yuan et al. 2003) RTP1 (Mast et al. 2010)
TRPC3	TRPC1, TRPC4, TRPC5 (Strubing et al. 2003) TRPC6, TRPC7 (Hofmann et al. 2002) Orai1 (Liao et al. 2007)	IP_3R (Kiselyov et al. 1999) CaM (Zhang et al. 2001) CSR (Bandyopadhyay et al. 2012) $G_{q/11,}$ PLCβ (Lockwich et al. 2001) PLCγ (Patterson et al. 2002) PMCA (Kim et al. 2006a) RACK1 (Bandyopadhyay et al. 2008) SERCA (Lockwich et al. 2001)	AP-2, clathrin, dynamin, synaptotagmin (Lockwich et al. 2008) Cav-1, Ezrin (Lockwich et al. 2001) Homer (Kim et al. 2006a) MxA (Lussier et al. 2005) RACK (Bandyopadhyay et al. 2008) SNARES, syntaxin, VAMP2 (Singh et al. 2004)
TRPC4	TRPC1 (Strubing et al. 2001) TRPC3, TRPC6(Strubing et al. 2003) TRPC5 (Hofmann et al. 2002)	Fyn (Odell et al. 2005) IP_3R, CaM (Tang et al. 2001) PLCβ (Tang et al. 2000) Protein 4.1 (Cioffi et al. 2005) SESTD1 (Miehe et al. 2010) STIM1 (Huang et al. 2006)	Cav-1 (Murata et al. 2007) Homer (Yuan et al. 2003) MxA (Lussier et al. 2005) NHERF (Tang et al. 2000) ZOI (Song et al. 2005)
TRPC5	TRPC1 (Strubing et al. 2001) TRPC4 (Hofmann et al. 2002)	IP_3R, CaM (Tang et al. 2001) NCS-1 (Hui et al. 2006) SESTD1 (Miehe et al. 2010) STIM1 (Huang et al. 2006)	AP-2, clathrin, dynamin (Goel et al. 2005) EB50, NHERF (Tang et al. 2000) Enkurin(Sutton et al. 2004) Homer (Yuan et al. 2003) MxA (Lussier et al. 2005) PI(3)K, PIP(5)K, Rac1 (Bezzerides et al. 2004) Stathmin (Greka et al. 2003)
TRPC6	TRPC1, TRPC4, TRPC5 (Strubing et al. 2003) TRPC2 (Chu et al. 2004) TRPC3, TRPC7	IP_3R, CaM, Calcineurin (Tang et al. 2001) FKBP12 (Kim and Saffen 2005)	Clathrin, dynamin (Goel et al. 2005) MxA (Lussier et al. 2005) PI(3)K, PTEN (Monet

(continued)

Table 2 (continued)

Channel	Other channels	Signaling proteins	Scaffolding and trafficking proteins
	(Hofmann et al. 2002) Orai1 (Liao et al. 2007)	Fyn (Hisatsune et al. 2004) $G_{\alpha q/11}$ (Bandyopadhyay et al. 2005) mAChR, PKC (Kim and Saffen 2005) PLCγ (Hirschler-Laszkiewicz et al. 2009) SERCA (Redondo et al. 2008)	et al. 2012) Rab9, Rab11 (Cayouette et al. 2010) RhoA (Tian et al. 2010) Syntaxin (Bandyopadhyay et al. 2005)
TRPC7	TRPC1 (Zagranichnaya et al. 2005) TRPC3 (Hofmann et al. 2002) TRPC5 (Saleh et al. 2008) TRPC6 (Hofmann et al. 2002)	cGMP-dependent protein kinase (Yuasa et al. 2011) IP_3R, CaM (Tang et al. 2001)	MxA (Lussier et al. 2005)

Channel–protein interactions are shown using methods such as immunoprecipitation, yeast two hybrid assays, GST fusion protein pull-down, and microscopy imaging techniques (e.g., immunofluorescence, TIRF, and FRET)
[a]Ambudkar and Singh (unpublished results)

of TRPC1. It is interesting to speculate that the level and type of physiological stimuli may have an impact on the channel regulation. Interaction between TRPC1 and IP_3R has been reported to be mediated by RhoA in endothelial cells (Mehta et al. 2003) and Homer1 in HEK293 cells (Kiselyov et al. 2007). Additionally, RhoA (Mehta et al. 2003) and other proteins such as Cav-1 (Ambudkar et al. 2006; Brazer et al. 2003; Lockwich et al. 2000) and β-tubulin (Bollimuntha et al. 2005a) affect surface expression of TRPC1. TRPC1 interaction with Cav-1 and RhoA is suggested to mediate its localization in lipid raft domains where TRPC1 channels are assembled and activated in response to store depletion (Pani et al. 2008). Further studies will be required to establish the exact contributions of each interacting protein in the regulation of TRPC1.

3.2 TRPC2

While the human *Trpc2* is a pseudogene and does not form a functional channel (Wes et al. 1995; Zhu et al. 1995), TRPC2 in other mammals (e.g., rat, bovine, and mouse) forms functional channels in different cell types and tissues, such as the vomeronasal organ (VNO), testis, spleen, and liver (Liman et al. 1999 ; Vannier et al. 1999; Wissenbach et al. 1998). Few studies have looked at the interactions between TRPC2 and other TRPC channels and various signaling proteins. When heterologously expressed in HEK293 cells, TRPC2 interacts with endogenous

Homer1 and IP_3R (Yuan et al. 2003), but not with other TRPCs (Hofmann et al. 2002). Nonetheless, TRPC2 has been shown to interact with TRPC6 and signaling proteins, erythropoietin receptor, IP_3R, and PLCγ in primary erythroblasts (Chu et al. 2004; Tong et al. 2004). Additionally, TRPC2 forms a signaling complex with the receptor-transporting protein 1 (RTP1), Homer1, and IP_3R in the VNO (Mast et al. 2010). Other signaling proteins that interact with TRPC2 include STIM1 (Huang et al. 2006) and CaM (Tang et al. 2001; Yildirim et al. 2003). TRPC2 has been reported to co-localize with anoctamin 1 in the vomeronasal epithelium (Dibattista et al. 2012), although the interaction between the two proteins has not been confirmed using other techniques such as immunoprecipitation, FRET and TIRF.

3.3 TRPC3

While TRPC3, TRPC6, and TRPC7 share considerable homology in their amino acid sequences, as well as modes of activation, their physiological properties and function are quite distinct (Owsianik et al. 2006; Putney 2005). Depending on the level of expression and its heteromeric interactions with other TRPC channels, TRPC3 can form both store-independent and store-dependent channels in different cell types. As shown in Table 2, TRPC3 interacts with almost every member of the TRPC subfamily, as well as TRPM4 (Park et al. 2008) and Orai1 (Liao et al. 2007; Woodard et al. 2010). A fairly comprehensive list of TRPC3-associated proteins was identified in an earlier proteomic study, including proteins associated with Ca^{2+} entry and signaling, neural growth, vesicle fusion, mitochondria, endocytosis, actin cytoskeleton, and microtubules (Lockwich et al. 2008). As noted above, TRPC1 + TRPC3 and TRPC1 + TRPC3 + TRPC7 contribute to SOCE. TRPC3 has been suggested to act concertedly with TRPC1 to mediate SOCE in H19-7 hippocampal neuronal cells (Wu et al. 2004). Store dependence of TRPC3 might also be mediated by its interactions with Orai1 (Liao et al. 2007) and STIM1, the latter likely dependent on an interaction of TRPC3 with TRPC1 (Yuan et al. 2007). In addition to activation via the G protein/PLC-mediated pathway, heteromeric TRPC3 + TRPC4 channels in porcine aortic endothelial cells are redox activated (Poteser et al. 2006). Further research is required to delineate the molecular interactions involved in regulating TRPC3 channel assembly and function.

As seen with TRPC1, TRPC3 also interacts with a number of key Ca^{2+} signaling proteins involved in receptor-stimulated Ca^{2+} mobilization, such as PIP_2 hydrolysis (PLCβ, $G_{q/11}$), IP_3R, and the calcium-sensing receptor (CSR) (Table 2). SERCA and PMCA pumps also co-immunoprecipitate with TRPC3 (Bandyopadhyay et al. 2005; Kiselyov et al. 2007; Lockwich et al. 2001, 2008). Further, scaffolding proteins such as Homer or RACK1 interact with TRPC3 and modulate its interaction with IP_3R (Bandyopadhyay et al. 2008; Kiselyov et al. 2007). A number of protein interactions are involved in plasma membrane localization of TRPC3 (further discussed below).

3.4 TRPC4

TRPC4 is most closely related to TRPC5, sharing 65 % amino acid identity, but both proteins diverge in the last 220 amino acids. There is general consensus that TRPC4 forms an SOC channel even though it has been shown to form constitutively active or store-independent channels in some studies (Parekh and Putney 2005; Venkatachalam and Montell 2007). Heteromeric interactions have been described between TRPC4 and other TRPCs (Table 2) (Alvarez et al. 2008; Ambudkar et al. 2006; Ambudkar and Ong 2007; Antoniotti et al. 2006; Chen et al. 2009; Cheung et al. 2011; Murata et al. 2007; Phelan et al. 2013; Poteser et al. 2006; Puram et al. 2011; Riccio et al. 2009; Sabourin et al. 2009; Sundivakkam et al. 2012; Woo et al. 2008; Zimmermann et al. 2011). As described above for TRPC1 and TRPC3, TRPC4 heteromultimerizes with TRPC6 and, via its direct interaction with STIM1, forms a TRPC4 + TRPC6 channel that is store-dependent (Yuan et al. 2007). In intestinal smooth muscle cells, TRPC4 and TRPC6 channels are simultaneously activated by muscarinic receptors and contribute independently to the muscarinic receptor-induced cation current. Therefore, TRPC4 and TRPC6 channels couple muscarinic receptors to depolarization of intestinal smooth muscle cells and voltage-activated Ca^{2+} influx and contraction, thereby accelerating small intestinal motility in vivo (Ambudkar 2009; Tsvilovskyy et al. 2009). The interaction between STIM1 and TRPC4 was proposed to be the activation mechanism of the heteromeric TRPC1 + TRPC4 channels in glomerular mesangial cells (Sours-Brothers et al. 2009). Another protein vital for TRPC4 activity is protein 4.1, which functionally links TRPC4 to the actin cytoskeleton and spectrin in endothelial cells (Cioffi et al. 2005). Protein 4.1 and another adaptor protein, SESTD1, have been proposed to stabilize TRPC4 in a macromolecular complex associated with the cytoskeleton. SESTD1 associates with both TRPC4 and TRPC5 via the CIRB domain and functions to couple TRPC channel activity to lipid signaling (Miehe et al. 2010).

Signaling proteins involved in interactions with TRPC4 include the PDZ-domain proteins NHERF and ZO1 via the "VTTRL" sequence in the C-terminus of TRPC4 and PLC (Tang et al. 2000), as well as fyn (Odell et al. 2005). The dynamic interplay between tyrosine kinases, TRPC4 and NHERF, regulates cell surface expression and activation of the channel. TRPC4 also associates with the caveolae where growth factor receptor signaling proteins as well as NHERF-binding proteins, such as ezrin, are localized (Torihashi et al. 2002). 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.

3.5 TRPC5

Heterologously expressed TRPC5 forms a non-selective channel that can be activated by receptor stimulation but not store depletion in HEK293 (Schaefer

et al. 2000), PC12 (Ohta et al. 2004), and murine stomach cells (Lee et al. 2003) or directly by Ca^{2+} in HEK293 cells (Blair et al. 2009; Gross et al. 2009). TRPC5 can potentially form multimeric channels with other TRPCs (Table 2), e.g., TRPC1 + TRPC5 in neurons, vascular endothelial cells, and vascular smooth muscle cells (Goel et al. 2002; Shi et al. 2012; Strubing et al. 2001). Heterologously expressed TRPC5 forms a heteromeric channel with TRPC4 (Schindl et al. 2008). TRPC5 also has the sequence "VTTRL" in its C-terminus that mediates its interaction with the PDZ-binding proteins, NHERF and ezrin/moesin/radixin-binding phosphoprotein 50 (EBP50) (Obukhov and Nowycky 2004; Tang et al. 2000). NHERF mediates TRPC5 association with PLCβ and also regulates surface expression of TRPC5, whereas EBP50 links the channel to the actin cytoskeleton and modulates its activation kinetics following cell stimulation. Two CaM-binding sites located in the C-terminus of TRPC5 are involved in modulating channel activity (Tang et al. 2001). While myosin light chain kinase (MLCK) and PKC have been shown to regulate TRPC5 function, it is not clear whether these kinases exert their effects directly on the channel or indirectly by modulating the status of the actin cytoskeleton. Inhibition of MLCK activity adversely impacts channel activation, whereas PKC regulates channel desensitization following agonist stimulation. Additionally, activation of MLCK by Ca^{2+}/CaM has been proposed to prolong channel activity by enhancing surface expression of TRPC5 (Kim et al. 2006b; Shimizu et al. 2006). Trafficking of TRPC5 to specific sites in the hippocampal neurons is determined by its interaction with the exocyst component protein stathmin-2, SNARE proteins, and other trafficking proteins such as dynamin, clathrin, and MxA (Goel et al. 2005; Greka et al. 2003). Moreover, the neuronal calcium sensor-1 (NCS-1) binds to the C-terminus of TRPC5 (Hui et al. 2006) and is involved in retardation of neurite outgrowth by TRPC5 homomeric channel (Bezzerides et al. 2004).

3.6 TRPC6

TRPC6 has been widely shown to be activated by DAG and not by internal Ca^{2+} store depletion (Dietrich et al. 2005; Putney 2005). Nonetheless, several studies report that activation of TRPC6 by store depletion is mediated by its association with Orai1 (Liao et al. 2007) and TRPC4 (which directly binds STIM1) (Yuan et al. 2007). Heteromeric TRPC6 channels have also been reported in different cell types, such as TRPC3 + TRPC6 in pontine neurons (Li et al. 2005) and prostate cancer epithelial cells (Thebault et al. 2006) and TRPC6 + TRPC7 in A7r5 cells (Maruyama et al. 2006). TRPC6 channel activity is determined via its interactions with different signaling proteins. The tyrosine kinase, fyn, interacts with TRPC6 and modulates channel activity via tyrosine phosphorylation in COS-7 cells (Hisatsune et al. 2004). Stimulation of neuronal PC12D cells with acetylcholine results in formation of a multiprotein complex of TRPC6, M1 mAChR and PKC, and DAG production. While DAG activates TRPC6, DAG-activated PKC phosphorylates the channel to inhibit it (Kim and Saffen 2005).

TRPC6 also undergoes trafficking to the plasma membrane, and several proteins that associate with the channel have a role in this process, such as enkurin (Sutton et al. 2004), actinin, actin, and drebrin (Goel et al. 2005), and endocytic vesicle-associated proteins (Goel et al. 2005; Lussier et al. 2005). TRPC6 also contains the conserved CIRB domain in the C-terminus, and CaM reportedly regulates TRPC6 activation (Tang et al. 2001; Yuan et al. 2003).

3.7 TRPC7

Since the first isolation of TRPC7 by screening the fetal brain and caudate nucleus cDNA libraries (Nagamine et al. 1998), there are relatively few studies that report its properties and function. Both store-dependent and store-independent modes of activation, as well as constitutive activation, have been reported for TRPC7 (Numaga et al. 2007). Multimeric TRPC1 + TRPC3 + TRPC7 channels function as SOC channels, whereas TRPC3 + TRPC7 channels appear to be DAG-activated channels, in HEK293 cells (Zagranichnaya et al. 2005). Additionally, function of TRPC7 has been reported to be modulated by cGMP-dependent protein kinase 1α (Yuasa et al. 2011), CaM, IP_3R, and PIP_2 (Ju et al. 2010; Mery et al. 2001; Tang et al. 2001; Yuan et al. 2003). Little is known about the mechanisms regulating the trafficking and localization of TRPC7, even though it has been shown to interact with IP_3R, CaM, and MxA (Table 2).

4 Regulation of TRPC Channel Function by Intracellular Ca^{2+} Store Depletion

As discussed above, all TRPC channels are activated in response to stimulation of plasma membrane receptors that result in PIP_2 hydrolysis. Some TRPCs are regulated by store depletion induced following stimulation by physiological agonists as well as treatment of cells with passively depleting agents such as thapsigargin and cyclopiazonic acid. Furthermore, in these cases, channel function is blocked by conditions that inhibit SOCE, such as the application of 1 μM Gd^{3+} and 10 μM 2APB. Typically, TRPC1 and TRPC4 have been suggested to be store-operated while TRPCs 3, 5, 6, and 7 have shown to be store-independent. The mechanisms by which store-independent regulation of TRPC channels occurs, presumably via PIP_2 hydrolysis or DAG, are not very well established. Here we will summarize the presently available data on the regulation of TRPC channels by store depletion.

4.1 Role of STIM1

Considerable progress has been made regarding the TRPC channels that contribute to SOCE. In 2005, STIM1 was identified as the ER calcium sensor that regulates

SOCE. STIM1 is diffusely localized in the ER in resting conditions, and upon Ca^{2+} store depletion, it aggregates and translocates to the periphery of the cells where it interacts with both Orai1 and TRPC channels in specialized ER-plasma membrane (PM) junctional domains. In these regions, the ER and plasma membrane come in close proximity to each other (Cheng et al. 2013; Hogan et al. 2010; Liou et al. 2005; Roos et al. 2005). The Orai channel family is comprised of three isoforms (Orais 1, 2, and 3), all of which have four transmembrane domains. Orai1 has been suggested to function as a tetramer (Hogan et al. 2010; Ji et al. 2008; Penna et al. 2008) and more recently as a hexamer based on crystal structure (Hou et al. 2012). The discovery of STIM1 and Orai1 led to the identification of the long sought-after components of the CRAC channel. STIM1 and Orai1 together are sufficient to reconstitute CRAC channel activity, with the C-terminal SOAR domain (aa 344–442) in STIM1 being the region involved in gating Orai1 and generating I_{CRAC} (Hogan et al. 2010; Yuan et al. 2009). Numerous reports have demonstrated that STIM1 also interacts with members of the TRPC channel family and that it is necessary for gating TRPC channels (Cheng et al. 2013; Lee et al. 2010). Furthermore, TRPC heteromers that contain either TRPC1 or TRPC4 can be activated by STIM1. Thus, TRPC3 or TRPC6, likely non-store-operated channels, can appear to be regulated by STIM1 if they are assembled in the channel with TRPC1 or TRPC4 (Huang et al. 2006). The critical role of STIM1 in TRPC regulation [discussed in reviews by Cheng et al. (2013), Worley et al. (2007), and Lee et al. (2010)] is shown by the following data: (1) STIM1 and TRPCs co-immunoprecipitate and this association increases following store depletion; (2) the binding of STIM1 and TRPC1 has been confirmed by GST-fusion protein pull-down assays; (3) TRPC-mediated Ca^{2+} entry in response to store depletion is completely abolished by the knockdown of endogenous STIM1; (4) co-expression of TRPC1 and STIM1 induces an increase in store depletion-induced Ca^{2+} influx as well as I_{SOC}; (5) endogenous TRPC function is suppressed by heterologous expression of dominant-negative STIM1 constructs; and (6) the STIM1D76A mutant, which induces constitutive Orai1 activation, also mediates spontaneous TRPC channel function. In aggregate, all these data provide convincing support that STIM1 regulates TRPC channel activation and function. Structure-function analysis of STIM1 has revealed crucial information regarding STIM1 domains involved in the interaction with TRPCs. The ERM (ezrin/radixin/moesin) domain (aa 251–535) located within the STIM1 cytosolic carboxyl terminus has been shown to bind selectively to some TRPC channels, e.g., TRPC1, TRPC2 and TRPC4, but not TRPC3, TRPC6, and TRPC7. As mentioned above, channels that cannot bind to STIM1 can be regulated by it if they are assembled in a heteromeric channel complex with TRPCs that bind STIM1. Nonetheless, it is notable that several studies with heterologous expression of TRPCs and STIM1 have failed to demonstrate the involvement of these channels in SOCE. It might be important to consider the assembly of TRPC channel complexes in such studies as other components might be essential in the regulation of these channels.

Binding of the ERM domain of STIM1 to TRPC channels is not sufficient for channel activation. A lysine-rich domain (referred to as polybasic tail or K domain)

located at the C-terminal end of STIM1 has been established as the region that is involved in gating TRPC channels. Deletion of the STIM1-K domain affected TRPC channel activity but not binding to STIM1. The mechanism underlying the gating of TRPC channels by STIM1 has been revealed in a study demonstrating that the positively charged lysine residues (^{684}KK^{685}) in STIM1 interact electrostatically with negatively charged conserved aspartate residues in TRPC1 (^{639}DD^{640}), which leads to gating of the channel (Zeng et al. 2008). When the negative charges in TRPC1 are neutralized by substituting lysine (K) with alanine (A), channel activation by STIM1 is blocked. Moreover, swapping the charges between TRPC1 and STIM1 induces recovery of channel gating and function, providing conclusive evidence for the gating of TRPC1 by STIM1. Remarkably, the negatively charged sequence in TRPC1 C-terminus is highly conserved among TRPC family members, including TRPC3, TRPC4, TRPC5, and TRPC6 (Zeng et al. 2008). Thus, it was proposed that other TRPCs also have the inherent capacity to be gated by STIM1, although not all TRPCs bind directly to STIM1. Further studies need to be carried out to conclusively establish which TRPCs can bind to and are gated by STIM1, especially with regards to endogenous TRPC channels. Such information is crucial for understanding how store-dependent TRPC channels are assembled and regulated.

4.2 Role of Orai1

A very significant finding reported by several groups of researchers is that TRPC channel activation is not only dependent on STIM1 but also requires Orai1. Conclusive findings show that stimulation of cells results in dynamic assembly of TRPC1, STIM1, and Orai1 in a ternary complex in the ER-PM junctional domains, which is required for the activation of both Orai1 as well as TRPC1 channels. The TRPC1–STIM1–Orai1 complex, associated with SOCE, can be detected in HSG cells (Ong et al. 2007), mouse pulmonary arterial smooth muscle cells (Ng et al. 2009), human parathyroid (Lu et al. 2010), human liver cell (Zhang et al. 2010), and rat kidney fibroblast (Almirza et al. 2012). Assembly of this complex is mediated via STIM1, as knockdown of STIM1 prevents clustering of TRPC1 with Orai1. Knockdown of TRPC1 results in attenuation of function, while knockdown of Orai1 or STIM1 results in complete loss of SOCE. Furthermore, overexpression of pore-deficient, dominant-negative mutants of Orai1 (R91W, E106Q) abrogate Ca^{2+} entry due to TRPC1-STIM1 (Cheng et al. 2008; Ong et al. 2007). The exact mechanism by which Orai1 determines TRPC function has been a matter of much debate. It was suggested that Orai1 can physically interact with the C- and N-termini of both TRPC3 and TRPC6 channels and modulate channel sensitivity to store depletion and STIM1 (Liao et al. 2007). Hence, these investigators proposed that the endogenous SOCE channel pore is contributed by TRPC channels with Orai1 functioning as the regulatory subunit. Alternatively, TRPC channels have been proposed to modify Orai1 function.

The key question of whether TRPC and Orai1 contribute to a single channel pore (formation of a heteromeric TRPC + Orai1 channel) or are two distinct channels which independently contribute to SOCE has been resolved recently for TRPC1 and TRPC5. In a cell line where endogenous TRPC1 contributes to SOCE, TRPC1 and Orai1 form two distinct channels: a relatively Ca^{2+}-selective channel mediating I_{SOC} is composed of STIM1/TRPC1 and a highly Ca^{2+}-selective channel mediating I_{CRAC} is formed by STIM1/Orai1 (Cheng et al. 2011). The smaller conductance of I_{CRAC} is masked by the larger STIM1/TRPC1-mediated current that gets activated under the same conditions. Hence, the I_{SOC} attributed to STIM1/TRPC1 includes a small contribution from STIM1/Orai1 I_{CRAC}. Further, native I_{CRAC} is detected when TRPC1 channel function is suppressed in these cells by expression of the STIM1-KK/EE mutant, which can gate Orai1 but not TRPC1. More importantly, Ca^{2+} entry through STIM1/Orai1 facilitates TRPC1 channel trafficking and triggers TRPC1 insertion into the plasma membrane. Membrane insertion of TRPC is attenuated by removal of extracellular Ca^{2+}, blocking I_{CRAC} with 1 μM Gd^{3+}, knockdown of Orai1 or overexpression of dominant-negative mutant of Orai1 (E106Q) that lacks a functional pore (Cheng et al. 2011). These data define the functional role of Orai1 and provide novel insights into the regulation and activation of TRPC1 in SOCE. Regulated surface insertion of TRPC1 by Orai1 can provide a rapid modulation and amplification of SOCE-facilitated Ca^{2+} signals that could selectively impact regulation of cell function (Cheng et al. 2013). Ca^{2+} entry via Orai1 has also been shown to facilitate TRPC5 activity (Gross et al. 2009). In this case, Ca^{2+} coming into the cell via Orai1 directly activates the TRPC5 channel. Detailed studies have not been done along these lines for other TRPCs to either demonstrate or rule out a secondary effect of Orai1 on channel function. It is important to note that heterologous expression might not yield similar data to that with endogenous channels, especially when several molecular components and regulatory mechanisms concertedly determine channel function.

5 Modulation of TRPC Channels by Membrane Trafficking

Localization of TRPC channels in specific plasma membrane microdomains allows the generation of precise intracellular Ca^{2+} signals that modulate downstream signaling events and consequent cell functions. The amplitude and duration of intracellular Ca^{2+} signals can be varied by regulating Ca^{2+} influx via TRPC channels, which can be enhanced by increasing the number of active channels at the cell surface either by driving channel trafficking to the plasma membrane or by prolonging channel retention at the cell surface. Major modes of regulating Ca^{2+} entry include constitutive and regulated vesicular trafficking mechanisms as well as the rates of protein synthesis and degradation. The constitutive and regulated trafficking processes determine the surface expression of TRPC channels by (1) increasing exocytosis and/or recycling to the plasma membrane or (2) reducing endocytosis and/or increasing channel retention in the plasma membrane.

5.1 TRPC1

Studies of the TRPC1 complex identified several interacting proteins that are involved in vesicle trafficking, membrane fusion, and cytoskeletal and actin rearrangement, such as clathrin, dynamin, Sec1, synapsin-2, Cav-1, and RhoA (Table 2). The TRPC1 signaling complex is localized in distinct cholesterol-rich plasma membrane domains known as lipid rafts. Disruption of lipid rafts with cholesterol-depleting agents like methyl-β-cyclodextrin (MβCD) decreased SOCE in salivary gland cells (Lockwich et al. 2000) and vascular smooth muscle cells (Bergdahl et al. 2003), suggesting lipid raft integrity is a prerequisite for TRPC1 localization and function. Cav-1 is a cholesterol-binding protein found within the caveolae, which are caveolin-containing lipid rafts present in the plasma membrane. Cav-1 plays an important role in the trafficking and function of TRPC1 (Brazer et al. 2003; Kwiatek et al. 2006; Lockwich et al. 2000; Pani et al. 2009, 2012). The present model proposes that Cav-1 functions as a scaffolding protein that facilitates assembly of the TRPC1 signaling complex and acts synergistically with Orai1 and STIM1 to regulate TRPC1 channel activity (Ong and Ambudkar 2012; Pani et al. 2009). In resting cells, TRPC1 is controlled by constitutive trafficking mechanisms. Following trafficking to the cell periphery, TRPC1 associates with Cav-1 but remains inactive and does not get inserted into the plasma membrane. When cells are stimulated by physiological agonists and the ER-Ca^{2+} stores are depleted, STIM1 translocates to the plasma membrane and activates the Orai1 channel. The Orai1-mediated Ca^{2+} influx drives the recruitment of TRPC1 into the plasma membrane. TRPC1 dissociates from Cav-1 and interacts with and is activated by STIM1. Dissociation of TRPC1 from Cav-1 is an essential step in the activation of TRPC1 by STIM1 since C-terminal ^{684}KK^{685} residues of STIM1 responsible for gating TRPC1 also releases the channel from Cav-1 (Pani et al. 2009; Zeng et al. 2008). In addition to Cav-1, Homer1 also interacts with TRPC1 in the C-terminus (aa 644–650), a region that lies just upstream of the STIM1-gating site (aa 639–640). Homer1 forms a dynamic complex with TRPC1 and IP_3R. Following cell stimulation, the TRPC1/Homer1/IP_3R complex disassembles, resulting in channel activation.

Local changes in the cytoskeleton or microtubules also contribute to the trafficking of TRPC1 (Bollimuntha et al. 2005a; Mehta et al. 2003). In retinal epithelial cells, β-tubulin has been shown to interact with TRPC1 and to be required for channel translocation to the plasma membrane (Bollimuntha et al. 2005a). RhoA, a monomeric GTPase protein responsible for actin cytoskeleton dynamics, associates with TRPC1 and IP_3R in endothelial cells following stimulation with thrombin. Assembly of the TRPC1/IP_3R complex, as well as trafficking to the plasma membrane, is dependent of RhoA and actin polymerization since SOCE is attenuated following treatment with C3 transferase protein that inactivates Rho or expression of a Rho dominant mutant (Mehta et al. 2003). Enkurin, a CaM-binding protein, interacts with TRPC1 and TRPC5 in sperm and has been suggested to function as an adaptor protein that tethers signaling proteins to TRPC channels (Sutton et al. 2004). Proteins involved in vesicle docking and fusion have also been

reported to interact with TRPC1 and regulate channel activity. Nevertheless, the relevance of these various components in the intracellular trafficking of TRPC1 has yet to be identified.

5.2 TRPC3

As described earlier for TRPC1, the interactions of TRPC3 with several proteins are vital for its proper trafficking and cellular localization. These include PLCγ (van Rossum et al. 2005), Cav-1 (Lockwich et al. 2001), VAMP2 (Singh et al. 2004), RFN24 (Lussier et al. 2008), and Homer1 (Kim et al. 2006a). Surface expression of the TRPC3 channel requires interaction with PLCγ and PIP_2, which anchors the channel in the plasma membrane (van Rossum et al. 2005). Homer1 has been reported to stabilize the interaction between TRPC3 and IP_3R, determining the rate of TRPC3 translocation to and retrieval from the plasma membrane (Kim et al. 2006a; Kiselyov et al. 2007). Both Homer1 and junctate may function synergistically to facilitate the interaction between TRPC3 and IP_3R which leads to channel activation. It is possible that the components involved in TRPC3 trafficking depend on the cell type and the spatial constraints within the cell.

Cell surface expression of TRPC3 is regulated by VAMP2-mediated fusion of mobile intracellular vesicles containing TRPC3 with the plasma membrane. Expression of TRPC3 in the plasma membrane increases following stimulation with carbachol, and this increase is abolished by treatment with tetanus toxin, which inhibits VAMP2 activity (Singh et al. 2004). Likewise, status of the actin cytoskeleton has also been reported to affect TRPC3 localization and function. Conditions that result in enhancement or stabilization of the cortical actin layer, such as treatment with jasplakinolide or calyculin A, promote internalization of TRPC3 signaling complex with a consequent decrease of TRPC3 function (Lockwich et al. 2001). TRPC3-interacting proteins may also influence the trafficking and surface expression of the channel. These include clathrin, dynamin, AP-2, syntaxin, synaptotagmin-1 (Lockwich et al. 2008), MxA (Lussier et al. 2005), and RACK1 (Bandyopadhyay et al. 2008) (Table 2). Additional studies are required to resolve the role of the TRPC3-interacting proteins involved in constitutive and regulated trafficking of the channel.

5.3 TRPC4

Although several studies have reported the association of TRPC4 with scaffolding and trafficking proteins (Table 2), the mechanisms regulating TRPC4 localization in the plasma membrane have not been fully elucidated. A dynamic interplay between tyrosine kinases, TRPC4, and NHERF regulates surface expression and activation of TRPC4 channels (Tang et al. 2000). The protein tyrosine kinase, fyn, phosphorylates TRPC4 following stimulation by the epidermal growth factor (EGF), increasing its interaction with NHERF, as well as its insertion into the

plasma membrane (Odell et al. 2005). As mentioned above, TRPC4 forms a heteromeric complex with TRPC1 to mediate SOCE in endothelial cells. Loss of Cav-1 impairs surface expression of both TRPC4 and TRPC1, significantly reduces association of the heteromeric complex with IP_3R, and inhibits agonist-induced Ca^{2+} entry in these cells. Hence, Cav-1 is proposed to function as a scaffold that facilitates the interactions between TRPC4, TRPC1, and IP_3R.

5.4 TRPC5

Proteomic analysis of TRPC5-binding partners revealed the interactions of TRPC5 with proteins involved in vesicle trafficking and scaffolding (Table 2), such as dynamin, clathrin, AP-2 (Goel et al. 2005), and MxA (Lussier et al. 2005). Interaction of TRPC5 with the exocyst component protein, stathmin 2, targets homomeric channels to the growth cone of hippocampal neurons (Greka et al. 2003). In resting neuronal cells, TRPC5 is localized in intracellular vesicles close to the plasma membrane. Following stimulation with growth factors, TRPC5-containing vesicles are rapidly translocated and inserted to the plasma membrane, thereby increasing channel function constitutively. Trafficking of TRPC5 and insertion into the plasma membrane requires phosphatidylinositide 3-kinase (PI(3)K), Rac1, and phosphatidylinositol 4-phosphate 5-kinase (PIP(5)K). Interestingly, Rac1 initiates the insertion of homomeric TRPC5 but not the heteromeric TRPC1 + TRPC5 channels into the plasma membrane. This may be due to homomeric channels being localized in the growth cones to modulate elongation, whereas heteromeric channels are localized in the neurites (Bezzerides et al. 2004). It is also shown that TRPC5 participates in a molecular complex with Rac1 in fibroblasts and kidney podocytes and Ca^{2+} influx mediated by TRPC5 activates Rac1 (Tian et al. 2010). In aggregate, these studies show that components of the TRPC5 signaling complex determine its physiological function by influencing channel trafficking, localization, and activation.

5.5 TRPC6

There is a paucity of information on the proteins that interact with TRPC6 and regulate its trafficking to and localization in the plasma membrane (Table 2). Surface expression of TRPC6 is enhanced following cell stimulation by muscarinic receptor agonists or passive depletion of the ER-Ca^{2+} stores by thapsigargin (Cayouette et al. 2004). The GTPases, Rab9 and Rab11, have been shown to regulate the intracellular trafficking of TRPC6 in HeLa cells (Cayouette et al. 2010). In cells cotransfected with Rab9, TRPC6 shows a diffuse localization through the cell as well as partial colocalization with Rab9 containing vesicles. However, when Rab11 is overexpressed, TRPC6 is predominantly present at the cell periphery. Surface expression of TRPC6, as well as the channel activity,

increases following the expression of a dominant-negative mutant of Rab9 (S21N) and Rab11, whereas channel activity decreases when dominant-negative mutant of Rab11 (S25N) is expressed. In aggregate, these data suggest that the intracellular trafficking of TRPC6 is through early endosomes and late endosomes, where the channel interacts with Rab9-containing vesicles and the channel is translocated to the plasma membrane via Rab11-containing vesicles (Cayouette et al. 2010). PI(3)K and PTEN have also been reported to regulate the trafficking and activation of TRPC6 channels. PTEN-dependent inhibition of PI(3)K reduced translocation of TRPC6 to the plasma membrane, as well as TRPC6-mediated Ca^{2+} influx in T6.11 cells. Previous studies have reported the interaction of TRPC6 with other proteins that are involved in vesicle trafficking, such as MxA (Lussier et al. 2005), RhoA (Tian et al. 2010), syntaxin (Bandyopadhyay et al. 2005), clathrin, and dynamin (Goel et al. 2005). MxA (which also interacts with other TRPCs except TRPC2) has been shown to modulate TRPC6-mediated Ca^{2+} entry in response to cell stimulation. The importance of such interactions in modulating surface expression and activity of TRPC6 remain to be fully delineated in future studies.

5.6 TRPC2 and TRPC7

There is relatively less information regarding the protein interactions and trafficking of TRPC2 and TRPC7. Similar to other TRPC channels, TRPC2 interacts with enkurin (Sutton et al. 2004) and Homer (Yuan et al. 2003). It has also been shown that the chaperone receptor-transporting protein 1 (RTP1) regulates the surface expression and channel activity of TRPC2 in HEK 293 cells. In cells cotransfected with RTP1, the surface expression of TRPC2, as well as the channel activity, is increased relative to cells expressing TRPC2 alone (Mast et al. 2010). A previous study demonstrates that TRPC7 interacts with MxA, a member of the dynamin superfamily (Lussier et al. 2005).

Conclusion

In summary, TRPC channels are regulated downstream from receptor-coupled PLC activation. These channels contribute to a wide variety of cellular function. Loss or gain of channel function has resulted in aberrant physiology in human and mouse. The physiological function and regulation of TRPC channels are influenced by their physical and functional interactions with numerous channels and proteins involved in the signaling, scaffolding, and trafficking processes. Further studies are required to delineate the exact steps involved in assembling TRPC channels with their accessory proteins to form functional signaling complexes in discrete ER-PM junctional regions. Understanding the various modes and mechanisms involved in TRPC channel function can provide potentially important targets for treatment of a number of diseases.

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