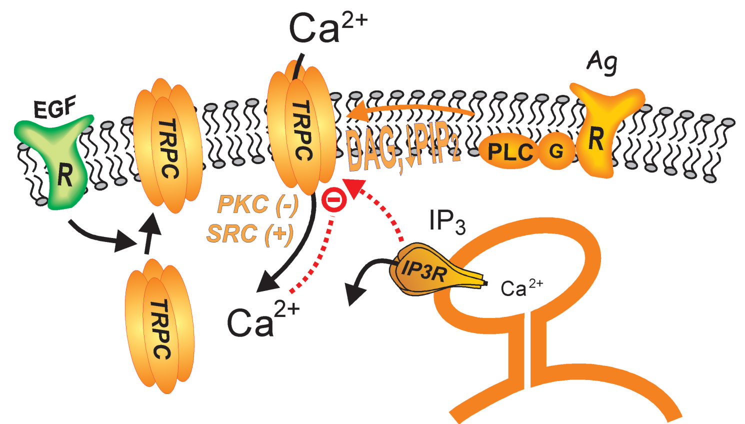
ISSN-1308-416X

Cell Membranes and Free Radical Research

Volume 1 Number 2 1 December 2008



EDITOR-IN-CHIEF
Mustafa Nazıroğlu, Isparta, TURKEY

Activation and Regulation of TRPC Cation Channels

James W. Putney, Jeremy T. Smyth, Mohamed Trebak[1], Loïc Lemonnier[2], Guillermo Vazquez[3], Gary S. Bird
[1]Cardiovascular Sciences, MC8, Albany Medical College, 47 New Scotland Avenue, Albany, NY 12208, USA
[2]Université de Lille 1, Villeneuve d'Ascq F-59650, Lille, France
[3]Department of Physiology and Pharmacology, University of Toledo College of Medicine, Toledo, OH 43614, USA

Introduction

The TRP ion channel superfamily is comprised of three major sub-families: TRPC, TRPM and TRPV (for review, and discussion of smaller TRP subfamilies, see (Ramsey et al., 2006)). Of all the TRPs, the TRPCs bear the closest structural and functional similarity to the founding Drosophila TRP. They are thus designated TRPC, the "C" indicating "canonical." Like Drosophila TRP, they are clearly activated downstream of phospholipase C, and like Drosophila TRP, the precise mechanism by which phospholipase regulates them is not in all cases clear. Nonetheless, it is known that this ion channel family subtends numerous important physiological processes, including activation of vascular and other smooth muscles (Dietrich et al., 2005), exocrine gland secretion (Liu et al., 2007), neuronal migration (Hui et al., 2006; Greka et al., 2003) to name a few. The TRPCs have also been shown to be sensitive targets for oxidative stress (Thyagarajan et al., 2001; Poteser et al., 2006; Miller, 2006), and thus could underlie or contribute to any number of pathological outcomes from oxidative stress exposure. It is thus important to understand how the TRPC channels function at a cellular and molecular level and how cellular signaling pathways regulate the actions of this important channel family.

Like their close relative Drosophila TRP, TRPCs appear to be activated downstream of phospholipase C. There are some reports that they can, under certain conditions, act as store operated channels, but this is controversial (Parekh & Putney, 2005). In this review, we will discuss TRPC activation and regulation by phospholipase C-dependent pathways, focussing mainly on findings from this laboratory; for a discussion of the issue of store-operated TRPCs, the reader is referred to (Parekh & Putney, 2005) and references therein. For a more comprehensive review of TRPs and their regulation, the reader is directed to any of a number of recent reviews (Abramowitz & Birnbaumer, 2008; Nilius et al., 2007; Voets & Nilius, 2007; Venkatachalam & Montell, 2007; Trebak et al., 2007; Miller, 2006; Michel, 2006; Nilius & Voets, 2005).

Activation of TRPCs

Activation of phospholipase Cßs by receptors coupled to Gq/11 involves a number of players and potential signals (Rhee, 2001; Exton, 1996), several of which have been implicated in activating or regulating TRPC channels. Phosphatidylinositol 4,5-bisphosphate (PIP2) is cleaved to diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). DAG activates downstream effectors, the most extensively documented and investigated being protein kinase C. IP3 binds to and activates IP3 receptors on the endoplasmic reticulum (ER) resulting in release of Ca2+. The depletion of ER Ca2+ leads to the activation of the Ca2+ sensor, STIM1 which in an unclear manner activates plasma membrane store-operated Orai Ca2+ channels (Frischauf et al., 2008).

Perhaps the most solidly established activator of TRPC channels is diacylglycerol, which has been shown to activate TRPC3, 6 and 7 (and possibly TRPC2 (Lucas et al., 2003)) by a mechanism that is independent of protein kinase C (Hofmann et al., 1999); protein kinase C in fact is a strong negative regulator of TRPCs, as discussed in a subsequent section. The simplest experimental demonstration of DAG activation comes from application of synthetic, membrane permeant diacylglycerols (Hofmann et al., 1999), the most common being oleyl acetyl glycerol (OAG). Activation by endogenous DAG can also be demonstrated by use of inhibitors of DAG metabolism, specifically by inhibiting DAG lipase or DAG kinase (Hofmann et al., 1999; Venkatachalam et al., 2003; Trebak et al., 2003a). There is considerable evidence that the activation by DAG does not, however, involve a direct action of DAG on the channels. First, regulation by DAG is lost in excised patches (Lemonnier et al., 2008) (but see (Hofmann et al., 1999)). Second, DAG activation of TRPC3 is lost in the absence of the tyrosine kinase, src (Vazquez et al., 2004b). Third, TRPC3 channels newly trafficked to the plasma membrane appear to have constitutive activity, but not the ability to be activated by DAG (Smyth et al., 2005).

The mechanism for activation of a structurally similar subgroup of TRPCs, specifically TRPC1, 4 and 5, is less clear. Unlike other TRPC channels, neither synthetic DAG nor DAG metabolism inhibitors activate this group (Schaefer et al., 2000; Venkatachalam et al., 2003). The other signaling product of phospholipase C, IP3, also does not seem to activate members of this group (Schaefer et al., 2000). There is evidence that Ca2+, acting through myosin light chain kinase, can activate TRPC5 (Shimizu et al., 2006), but this is not likely the sole activator since TRPC5 can be activated in a sustained manner with strong intracellular Ca2+ buffering (10 mM BAPTA, (Trebak et al., 2009)). Trebak et al. noted that in addition to the for-

mation of DAG and IP3, phospholipase C activation also induces a decrease in membrane PIP2 (Trebak et al., 2009). Accordingly, three different drugs that cause PIP2 depletion by inhibiting PIP kinase all activated TRPC5 channels in TRPC5-transfected HEK293 cells. These same drugs inhibited TRPC3 activity. However, when TRPC channel activity was investigated at the single channel level in excised patches, TRPC3, 5, 6 and 7 were all strongly activated by PIP2 (Trebak et al., 2009; Lemonnier et al., 2008). This led to an hypothesis according to which PIP2 regulates certain TRPC channels by a dual mechanism. For TRPC5, it was proposed that PIP2 is required for channel activity probably through a direct interaction with the channel, but also acts as a negative regulator through interaction with another protein. This latter protein may be lost in the excised patch, such that only the activating function of PIP2 is observed.

Regulation of TRPCs

Trafficking. Both TRPC5 (Bezzerides et al., 2004) and TRPC3 (Smyth et al., 2005) show regulated trafficking into and out of the plasma membrane, and this may be a general phenomenon for other TRPCs as well. For TRPC3, OAG or activators of phospholipase C do not affect trafficking; rather, only tyrosine kinase-linked growth factors, such as EGF activate trafficking. TRPC3 appears to undergo rapid reversible constitutive trafficking, and it may be that EGF causes stabilization of the channel in the plasma membrane. Interestingly, newly translocated TRPC3s showed constitutive activity but apparently could not be activated by OAG (Smyth et al., 2005).

IP3 Receptor. There is considerable biochemical evidence for interaction between IP3 receptors and the C-terminus of TRPCs (Kiselyov et al., 1998; Kiselyov et al., 1999; Tang et al., 2001). This was interpreted as a mechanism through which intracellular stores could communicate with plasma membrane TRPC channels, i.e., a mechanism for store-operated Ca2+ entry. However, a number of studies, examining the activation of expressed TRPC channels, have failed to find any functional requirement for IP3 or for the IP3 receptor (Trebak et al., 2003a; Hofmann et al., 1999). A study by Vazquez et al. (Vazquez et al., 2006) examined the activation and regulation of native TRPC7 channels in DT40 cells, an avian B-lymphocyte line. The activity of these channels was lost following knockout of the TRPC7 gene, and also in a line lacking IP3 receptors. TRPC7 activity could be restored by transfecting either cell type with cDNA encoding human TRPC7. However, when a low concentration of plasmid was used, successful restoration of TRPC7 activity was only observed in the TRPC7 knockout cells, not in the IP3 knockout cells. This result, and other findings in the study, indicate that at physiological levels of expression, TRPC7 activity depends in some manner on IP3 receptors. At higher levels of expression, this dependence is lost. Nonetheless, it was clear from the study of Vazquez et al. (Vazquez et al., 2006) that even when TRPC7 activity did depend upon IP3 receptors, the mechanism of its activation did not require depletion of intracellular stores. The function of IP3 receptors in TRPC channel activation is not known, but given the well documented direct interaction of the receptors and channels it may be that IP3 receptors play a role in organizing channels in the proximity of receptor-regulated phospholipase C.

Protein Kinase C. It appears that all TRPCs are negatively regulated by protein kinase C (Trebak et al., 2003a; Venkatachalam et al., 2003; Trebak et al., 2005; Kwan et al., 2005) (but see (Saleh et al., 2008)). This likely provides a negative feedback when activation occurs through the phospholipase C pathway. The phosphorylation site was identified by Trebak et al. (Trebak et al., 2005) as a serine at position 712 in the human sequence. This is a highly conserved site among TRPCs, and lies just downstream of the last transmembrane domain in a region thought to be responsible for interacting with PIP2.

src. TRPC3 activation by DAG absolutely depends upon the tyrosine kinase, src (Vazquez et al., 2004b). Pharmacological inhibitors of src blocked TRPC3 activation by OAG, as did transfection with a dominant-negative mutant of src. When TRPC3 was expressed in a src-deficient cell line, it could not be activated by OAG unless co-expressed with src. Kawasaki et al. (Kawasaki et al., 2006) presented evidence that src phosphorylates tyrosine in position 226 in the N-terminus of TRPC3, and that this phosphorylation if essential for activity. How this action of src relates to regulation of TRPC3 activity under physiological conditions is not known.

Calcium. There is considerable evidence for Ca2+ regulation of TRPC channels (Obukhov et al., 1998; Trebak et al., 2003b). Calcium is thought to bind to calmodulin which in turn interacts with the C-terminus of TRPCs in an inhibitory manner (Zhang et al., 2001; Tang et al., 2001; Singh et al., 2002); however, there is evidence for calmodulin-independent inhibition of the related channel, Drosophila TRPL (Obukhov et al., 1998). Interestingly, Boulay et al. presented evidence that Ca2+/calmodulin can activate TRPC6 (Boulay, 2003), raising the possibility that different TRPCs may be regulated by Ca2+ in distinct ways. Shi et al. (Shi et al., 2004) found that TRPC6 was bimodally regulated. Low concentrations of Ca2+, acting on calmodulin, were required for channel activity, while higher concentrations were inhibitory. In experiments examining single channel activity, they demonstrated that TRPC6 channels were activated by Ca2+-calmodulin, while the highly structurally related TRPC7 channels were inhibited.

It would not be surprising for intracellular Ca2+ to negatively regulate TRPC channels, given the general consensus that they function as Ca2+ permeant channels, and that Ca2+ entering cells through TRPCs acts to activate important downstream processes (Birnbaumer et al., 1996; Vazquez et al., 2004a; Li et al., 2005). As a non-selective cation channel, however, a TRPC channel is at best an inefficient means of introducing Ca2+ into cells. Thus, physiologically the more important consequence of TRPC activation may be the ensuing depolarization which in turn may activated voltage-dependent conductances (Soboloff et al., 2005). In fact, much of the Ca2+ signal measured after activation of expressed TRPCs may arise secondarily from activation of a Na+-Ca2+ exchanger (Rosker et al., 2004). However, there is clear evidence that Ca2+ entering through TRPC channels exerts close proximity regulation of the channels themselves. Lemonnier et al. in studies of TRPC7 channels expressed in HEK293 cells observed that treatment of the cells with the sarcoplasmic-endoplasmic reticulum Ca2+ ATPase (SERCA) inhibitor, thapsigargin, substantially inhibited the OAG-activated currents (Lemonnier et al., 2006). Thapsigargin also inhibited OAG-activated currents in TRPC3-expressing cells, suggesting that this may be a general phenomenon for TRPC channels (or perhaps OAG-activated TRPC channels). Inhibition of TRPC7 by thapsigargin was not seen when Ca2+ was omitted from the bathing solution, or when cell membrane potential was held at positive potentials, reducing the driving force for Ca2+ entry. Inhibition of calmodulin by calmidazolium, or disruption of the actin cytoskeleton by cytochalasin B prevented the inhibition by thapsigargin. This indicates that Ca2+ entering the cell through TRPC7 channels has the capacity to inhibit the channels through a mechanism dependent on calmodulin and on cellular substructure, but this inhibition is usually attenuated by the Ca2+ buffering activity of SERCA pumps. Two observations indicate that the domain of this Ca2+ regulation must be exceedingly small. First, reducing the apparent single channel currents by submaximal concentrations of low affinity inhibitors reduced the dependency on SERCA. Second, the effects of thapsigargin were observed in the presence of 10 mM BAPTA Ca2+ buffer (Lemonnier et al., 2006).

Conclusion

This brief review has attempted to summarize work, primarily from the authors' laboratory, on diverse mechanisms for activation and regulation of TRPC channels. These channels are expressed in a wide variety of tissues; yet, with the possible exception of smooth muscles, little is known of their physiological functions in humans. Mouse models for some of the TRPCs have been described with interesting phenotypes (Freichel et al., 2004; Freichel et al., 2005; Liu et al., 2007; Dietrich et al., 2005). Information from single knockout models can be misleading because each TRPC apparently has one or more homolog that can substitute functionally (for example, (Dietrich et al., 2005)). We can look forward in the future to new and useful information on the roles of these interesting channels, and to a better understanding of how their complex modes of regulation can be exploited to manipulate their function to clinical advantage.

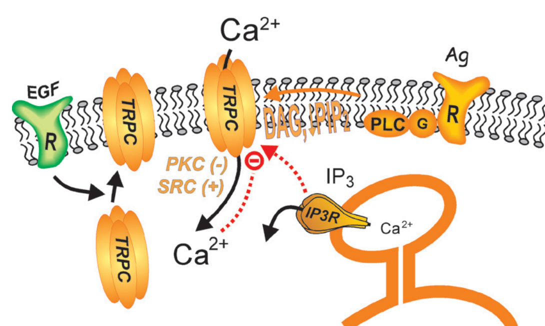
Acknowledgements

Some of the work described in this review was supported by the Intramural Research Program, National Institute of Environmental Health Sciences, National Institutes of Health, project number Z01 ES090087.

Figure Legend

Figure 1: Activation and regulation mechanisms for calcium-permeable TRPC cation channels. TRPC channels can be activated by DAG, or possibly as a result of loss of PIP2 following agonist (Ag) activation of phospholipase C (PLC) by a G-protein-coupled (G) pathway. In some instances, this activation mode requires the tyrosine kinase, Src (Vazquez et al., 2004b), and is negatively regulated by protein kinase C (PKC) (Trebak et al., 2005; Okada et al., 1999; Ahmmed et al., 2004; Trebak et al., 2003a; Venkatachalam et al., 2003). Regulation of TRPCs by Ca2+, entering through the channels, is complex, but generally high cytoplasmic Ca2+ inhibits TRPC function (Lemonnier et al., 2006). The activation of PLC leads to the production of IP3 which activates the IP3 receptor (IP3R) causing release of Ca2+ from a critical component of the endoplasmic reticulum. As to whether this release of Ca2+ activates TRPC channels is controversial (Parekh & Putney, 2005); however, there is evidence that some mode of interaction between the IP3 receptor and TRPC channels is involved in their activation (Vazquez et al., 2006). Left: Channels sequestered in a vesicular compartment can be translocated to the plasma membrane in response to growth factor (EGF) whence the expression of their constitutive activity may contribute to membrane signaling and electrical properties (Smyth et al., 2005).

Activation and Regulation of Calcium-permeable TRPC Cation Channels



References

Abramowitz J & Birnbaumer L. 2009. Physiology and pathophysiology of canonical transient receptor potential channels. FASEB J. 23: 298-327.

Ahmmed GU, Mehta D, Vogel S, Holinstat M, Paria BC, Tiruppathi C, & Malik AB 2004). Protein kinase Calpha phosphorylates the TRPC1 channel and regulates store-operated Ca2+ entry in endothelial cells. J Biol Chem 279: 20941-20949.

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.

Birnbaumer L, Zhu X, Jiang M, Boulay G, Peyton M, Vannier B, Brown D, Platano D, Sadeghi H, Stefani E, & Birnbaumer M. 1996. On the molecular basis and regulation of cellular capacitative calcium entry: Roles for Trp proteins. Proc Nat Acad Sci USA 93: 15195-15202.

Boulay G. 2003. Ca2+-calmodulin regulates receptor-operated Ca2+ entry activity of TRPC6 in HEK-293 cells. Cell Calcium 32:201-207.

Dietrich A, Mederos YS, 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.

Exton JH. 1996. Regulation of phosphoinositide phospholipases by hormones, neurotransmitters, and other agonists linked to G proteins. Ann Rev Pharmacol Toxicol 36:481-509.

Freichel M, Philipp S, Cavalie A, & Flockerzi V. 2004. TRPC4 and TRPC4-deficient mice. Novartis Found Symp 258: 189-199.

Freichel M, Vennekens R, Olausson J, Stolz S, Philipp SE, Weissgerber P, & Flockerzi V. 2005. Functional role of TRPC proteins in native systems: implications from knockout and knock-down studies. J Physiol 567:59-66.

Frischauf I, Schindl R, Derler I, Bergsmann J, Fahrner M, & Romanin C. 2008. The STIM/Orai coupling machinery. Channels (Austin) 2: 261-268.

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.

Hofmann T, Obukhov AG, Schaefer M, Harteneck C, Gudermann T, & Schultz G. 1999. Direct activation of human TRPC6 and TRPC3 channels by diacylglycerol. Nature 397:259-262.

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.

Kawasaki BT, Liao Y, & Birnbaumer L. 2006. Role of Src in C3 transient receptor potential channel function and evidence for a heterogeneous makeup of receptor- and store-operated Ca2+ entry channels. Proc Natl Acad Sci U S A 103:335-340.

Kiselyov K, Mignery GA, Zhu MX, & Muallem S. 1999. The N-terminal domain of the IP3 receptor gates store-operated hTrp3 channels. Mol Cell 4:423-429.

Kiselyov K, Xu X, Mozhayeva G, Kuo T, Pessah I, Mignery G, Zhu X, Birnbaumer L, & Muallem S. 1998. Functional interaction between InsP3 receptors and store-operated Htrp3 channels. Nature 396:478-482.

Kwan HY, Huang Y, & Yao X. 2006. Protein kinase C can inhibit TRPC3 channels indirectly via stimulating protein kinase G. J Cell Physiol. 207:315-321.

Lemonnier L, Trebak M, Lievremont JP, Bird GS, & Putney JW. 2006. Protection of TRPC7 cation channels from calcium inhibition by closely associated SERCA pumps. FASEB J 20:503-505.

Lemonnier L, Trebak M, & Putney JW, Jr. 2008. Complex regulation of the TRPC3, 6 and 7 channel subfamily by diacylglycerol and phosphatidylinositol-4,5-bisphosphate. Cell Calcium 43:506-514.

Li S, Gosling M, & Poll C. 2005. Determining the functional role of TRPC channels in primary cells. Pflugers Arch 451:43-52.

Liu X, Cheng KT, Bandyopadhyay BC, Pani B, Dietrich A, Paria BC, Swaim WD, Beech D, Yildrim E, Singh BB, Birnbaumer L, & Ambudkar IS. 2007. Attenuation of store-operated Ca2+ current impairs salivary gland fluid secretion in TRPC1(/) mice. Proceedings of the National Academy of Sciences 104:17542-17547.

Lucas P, Ukhanov K, Leinders-Zufall T, & Zufall F. 2003. A diacylglycerol-gated cation channel in vomeronasal neuron dendrites is impaired in TRPC2 mutant mice: mechanism of pheromone transduction. Neuron 40:551-561.

Michel MC. 2006. Transient receptor potential (TRP) channels as drug targets. Naunyn Schmiedebergs Arch Pharmacol 373:271-272.

Miller BA. 2006. The role of TRP channels in oxidative stress-induced cell death. J Membr Biol 209:31-41.

Nilius B, Owsianik G, Voets T, & Peters JA. 2007. Transient receptor potential cation channels in disease. Physiol Rev 87: 165-217.

Nilius B & Voets T. 2005. TRP channels: a TR(I)P through a world of multifunctional cation channels. Pflugers Arch. 45:1-10.

Obukhov AG, Schultz G, & Lückhoff A. 1998. Regulation of heterologously expressed transient receptor potential-like channels by calcium ions. Neurosci 85: 487-495.

Okada T, Inoue R, Yamazaki K, Maeda A, Kurosaki T, Yamakuni T, Tanaka I, Shimizu S, Ikenaka K, Imoto K, & Mori Y. 1999. Molecular and functional characterization of a novel mouse transient receptor potential protein homologue TRP7. Ca2+-permeable cation channel that is constitutively activated and enhanced by stimulation of G protein-coupled receptor. J Biol Chem 274:27359-27370.

Parekh AB & Putney JW. 2005. Store-operated calcium channels. Physiol Rev 85: 757-810.

Poteser M, Graziani A, Rosker C, Eder P, Derler I, Kahr H, Zhu MX, Romanin C, & Groschner K. 2006. TRPC3 and TRPC4 associate to form a redox-sensitive cation channel. Evidence for expression of native TRPC3-TRPC4 heteromeric channels in endothelial cells. J Biol Chem 281, 13588-13595.

Ramsey IS, Delling M, & Clapham DE. 2006. An introduction to TRP channels. Annual Review of Physiology 68:619-647.

Rhee SG. 2001. Regulation of phosphoinositide-specific phospholipase C. Ann Rev Biochem 70:281-312.

Rosker C, Graziani A, Lukas M, Eder P, Zhu MX, Romanin C, & Groschner K. 2004. Ca(2+) signaling by TRPC3 involves Na(+) entry and local coupling to the Na(+)/Ca(2+) exchanger. J Biol Chem 279:13696-13704.

Saleh SN, Albert AP, Peppiatt-Wildman CM, & Large WA. 2008. Diverse properties of store-operated TRPC channels activated by protein kinase C in vascular myocytes. J Physiol (Lond) 586:2463-2476.

Schaefer M, Plant TD, Obukhov AG, Hofmann T, Gudermann T, & Schultz G. 2000. Receptor-mediated regulation of the nonselective cation channels TRPC4 and TRPC5. J Biol Chem 275:17517-17526.

Shi J, Mori E, Mori Y, Mori M, Li J, Ito Y, & Inoue R. 2004. Multiple regulation by calcium of murine homologues of transient receptor potential proteins TRPC6 and TRPC7 expressed in

HEK293 cells. J Physiol 561:415-432.

Shimizu S, Yoshida T, Wakamori M, Ishii M, Okada T, Takahashi M, Seto M, Sakurada K, Kiuchi Y, & Mori Y. 2006. Ca2+-calmodulin-dependent myosin light chain kinase is essential for activation of TRPC5 channels expressed in HEK293 cells. J Physiol 570:219-235.

Singh BB, Liu X, Tang J, Zhu MX, & Ambudkar IS. 2002. Calmodulin regulates Ca2+-dependent feedback inhibition of store-operated Ca2+ influx by interaction with a site in the C terminus of TrpC1. Mol Cell 9:739-750.

Smyth JT, Lemonnier L, Vazquez G, Bird GS, & Putney JW. 2005. Dissociation of regulated trafficking of TRPC3 channels to the plasma membrane from their activation by phospholipase C. J Biol Chem 281:11712-11720.

Soboloff J, Spassova M, Xu W, He LP, Cuesta N, & Gill DL. 2005. Role of endogenous TRPC6 channels in Ca2+ signal generation in A7r5 smooth muscle cells. J Biol Chem. 280: 39786-39794

Tang J, Lin Y, Zhang Z, Tikunova S, Birnbaumer L, & Zhu MX. 2001. Identification of common binding sites for calmodulin and inositol 1,4,5-trisphosphate receptors on the carboxy termini of Trp channels. J Biol Chem 276: 21303-21310.

Thyagarajan B, Poteser M, Romanin C, Kahr H, Zhu MX, & Groschner K. 2001. Expression of Trp3 determines sensitivity of capacitative Ca2+ entry to nitric oxide and mitochondrial Ca2+ handling. Evidence for a role of Trp3 as a subunit of capacitative Ca2+ entry channels. J Biol Chem 276:48149-48158.

Trebak M, Bird GStJ, McKay RR, Birnbaumer L, & Putney JW. 2003a. Signaling mechanism for receptor-activated TRPC3 channels. J Biol Chem 278:16244-16252.

Trebak M, Hempel N, Wedel BJ, Smyth JT, Bird GS, & Putney JW. 2005. Negative regulation of TRPC3 channels by protein kinase C-mediated phosphorylation of serine 712. Mol Pharmacol 67:558-563.

Trebak M, Lemonnier L, DeHaven WI, Wedel BJ, Bird GS, & Putney JW, Jr. (2009). Complex functions of phosphatidylinositol 4,5-bisphosphate in regulation of TRPC5 cation channels. Pflugers Arch 457:757-769.

Trebak M, Lemonnier L, Smyth JT, Vazquez G, & Putney JW, Jr. 2007. Phospholipase C-coupled receptors and activation of TRPC channels. Handb Exp Pharmacol 593-614.

Trebak M, Vazquez G, Bird GStJ, & Putney JW. 2003b. The TRPC3/6/7 subfamily of cation channels. Cell Calcium 33:451-461.

Vazquez G, Bird GS, Mori Y, & Putney JW. 2006. Native TRPC7 Channel Activation by an Inositol Trisphosphate Receptor-dependent Mechanism. J Biol Chem 281:25250-25258.

Vazquez G, Wedel BJ, Aziz O, Trebak M, & Putney JW. 2004a. The mammalian TRPC cation channels. Biochim Biophys Acta 1742:21-36.

Vazquez G, Wedel BJ, Kawasaki BT, Bird GS, & Putney JW. 2004b. Obligatory role of Src kinase in the signaling mechanism for TRPC3 cation channels. J Biol Chem 279:40521-40528.

Venkatachalam K & Montell C. 2007. TRP channels. Annu Rev Biochem 76:387-417.

Venkatachalam K, Zheng F, & Gill DL. 2003. Regulation of Canonical Transient Receptor Potential (TRPC) Channel Function by Diacylglycerol and Protein Kinase C. J Biol Chem 278:29031-29040.

Voets T & Nilius B. 2007. Modulation of TRPs by PIPs. J Physiol (Lond) 582;939-944.

Zhang Z, Tang J, Tikunova S, Johnson JD, Chen Z, Qin N, Dietrich A, Stefani E, Birnbaumer L, & Zhu MX (2001). Activation of Trp3 by inositol 1,4,5-trisphosphate receptors through displacement of inhibitory calmodulin from a common binding domain. Proc Nat Acad Sci USA 98, 3168-3173.