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The integrative function of TRPC channels

Kirill Kiselyov[1], Randen L Patterson[2]

[1]Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA, [2]Department of Biology, The Pennsylvania State University, University Park, PA

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1. ABSTRACT

TRPC is a subfamily of Transient Receptor Potential channels that have the highest degree of homology to the Drosophila photoreceptors' TRP. TRPC open in response to stimulation of plasma membrane receptors that activate phospholipase C, triggering transmembrane Ca^{2+} influx. TRPC activity has been directly implicated in regulation of vascular tone, kidney filtration, acrosomal reaction and pheromone recognition. As humans contain six TRPC channels, which form homo- and hetero-tetramers, TRPCs are capable of forming multiple channels of varying current/voltage relationships and activation properties. This allows TRPC to participate in an array of intercellular pathways induced by chemical mediators including hormones, neurotransmitters and growth factors. The strength of TRPC response to stimulation is modulated by several factors such as covalent modification, interaction with auxiliary proteins and changes in the lipid environment. The existence of several modulatory inputs that converge on TRPC enables integration of various stimuli and differentiation of Ca^{2+} signaling in specific tissues. This synthesizes the current literature describing the known functions and phenomenology associated with TRPC channels, with a specific focus on the activation and modulatory mechanisms. We suggest that the polymodal regulation of TRPC channels is likely to explain many specific aspects of TRPC behavior in different tissues.

2. NATIVE TRPC

A number of hormones, neurotransmitters and growth factors exert their effects by initiating an increase in cytoplasmic Ca^{2+} in the target cells (1, 2). The spiking cytoplasmic Ca^{2+} changes the activity of Ca^{2+} binding proteins that control a variety of cellular processes including membrane vesicle fusion, electrolyte secretion, and gene expression. These Ca^{2+} spikes are triggered by activation of plasma membrane receptors; hormones and neurotransmitters usually act through G protein couple receptors, while growth factors employ receptor tyrosine kinases. The stimulated receptors activate phospholipase C (PLC) gamma or beta, which break down the minor membrane lipid phosphatydil inositol (4,5)-bisphosphate (PIP_2) and liberate two potent second messengers: inositol (1,4,5)-trisphosphate (IP_3) and diacyl glycerol (DAG). IP_3 diffuses into cytosol and activates the IP_3 receptor (IP_3R) Ca^{2+} release channel, which resides in the membranes of endoplasmic reticulum (ER), the largest intracellular Ca^{2+} pool. The IP_3R opening spills the ER Ca^{2+} into cytoplasm initiating the Ca^{2+} signal (1, 2). It is becoming increasingly clear that temporal characteristics of Ca^{2+} spikes are important for specificity of the signal, and that frequency of the spikes may encode which exact cellular function is being initiated (3). In order to guarantee fidelity of the Ca^{2+} signal, the cells possess powerful Ca^{2+} extrusion

mechanism that ends the Ca^{2+} rise allowing repetitive oscillatory signal, which is the main form of Ca^{2+} signal under the physiological levels of stimulation. A large fraction of cytoplasmic Ca^{2+} is exported to extracellular space by plasma membrane Ca^{2+} ATPase or returned to the ER by the sarcoplasmic/endoplasmic Ca^{2+} ATP-ase (SERCA), and thus the Ca^{2+} release is accompanied by activation of Ca^{2+} influx through the plasma membrane. It is thought that at least a fraction of such current is activated by a signal from the depleted intracellular Ca^{2+} stores (i.e. store-operated Ca^{2+} entry (SOCE)) (4). The search for the ion channels that mediate this influx proved to be one of the most exciting challenges for cell physiologists during the last 20 years.

Among several other channels, TRPC channels have emerged as possible candidates for the role of the Ca^{2+} channels that mediate the receptor operated Ca^{2+} influx. The original notion that TRPC might be such channels stems from the fact that the founding member of the entire TRP superfamily, the Drosophila photoreceptor Transient Receptor Potential channel, is activated as a result of PIP_2 breakdown. All TRPC channels are activated in the same manner, as is native Ca^{2+} entry. Indeed, several mammalian cell types possess native channels that resemble recombinant TRPC channels and specific suppression of several TRPC channels inhibits native receptor or SOCE, as well as the cellular functions that are thought to depend on such influx (discussed below). The following section will detail the physiological processes where native TRPC function has been implicated.

3. TRPC CHANNELS IN MAMMALIAN PHYSIOLOGY

The original observations of native TRPC1 activity were obtained in human submandibular gland cells, in which PLC stimulation or passive store depletion activated a nonselective cation channel whose properties were similar to that or recombinant TRPC1. Western blotting and PCR studies confirm TRPC1 expression in these cells and expression of the pore defective dominant negative TRPC1 mutant suppresses native receptor induced Ca^{2+} influx (5). Since then, the direct contribution of TRPC1 into native Ca^{2+} influx was confirmed in smooth muscle cells and endothelial cells using TRPC1 antibodies that blocked the Ca^{2+} influx (6-8). The functional role of TRPC1 in neurons was confirmed by the fact that TRPC1 inhibition blocks the mGluR1-evoked excitatory postsynaptic conductance in Purkinje cells (9). TRPC1 anti-sense knockdown inhibited bFGF induced Ca^{2+} signaling in neural stem cells (10) and Ca^{2+} entry stimulated by DAG and store depletion in HSY cells (11). siRNA techniques confirm contribution of TRPC1 in receptor and depletion induced Ca^{2+} entry in HEK 293 cells (12, 13), intestinal epithelial cells (14, 15), keratinocytes (16) and human mesangial cells (17) and into aromatic amino acid induced Ca^{2+} oscillations (18). Thus TRPC1 appears to be the main candidate for the receptor induced Ca^{2+} entry channel.

TRPC2 is abundantly and specifically expressed in vomeronasal organ (19-21), indicating that TRPC2 is involved in pheromone recognition and, indeed, TRPC2 deficient mice display abnormal gender specific and social response (22, 23). The role of TRPC2 in receptor-dependent Ca^{2+} influx in native tissues was demonstrated in experiments with sperm in which TRPC2 mediates Ca^{2+} influx that drives acrosomal reaction (24). Anti-sense suppression of TRPC2 also inhibited receptor induced Ca^{2+} influx in fibroblasts (25). As TRPC2 is a pseudogene in humans (26, 27), it is likely that the role of TRPC2 in humans has been incorporated by other TRPC members.

TRPC3 is perhaps the most studied TRPC channel. Native TRPC3 activity was demonstrated in pontine neurons (28), heart muscle (29), LNCaP prostate cancer cells (30) and smooth muscle (31). A role of TRPC3 in native receptor induced Ca^{2+} entry has been also inferred from transient knock-down experiments. Reductions of spontaneous Ca^{2+} entry in human T lymphocytes was shown to be associated with damage to TRPC3 gene (32). Additionally, genetic deletion of PLCγ from avian B-cells resulted in the loss of Ca^{2+} entry, which was linked to TRPC3 (33). Further, TRPC3 anti-sense suppressed receptor dependent Ca^{2+} entry in osteoblastic cells (34, 35). The same approach resulted in suppression of stimulation dependent depolarization, contraction and Ca^{2+} influx in smooth muscle cells (36, 37) and in rat small mesenteric arteries (38). As was discussed for TRPC1, siRNA mediated TRPC3 suppression inhibited both receptor and depletion induced Ca^{2+} influx in HEK 293 cells (12, 13), TNF-alpha activated Ca^{2+} influx in airway myocytes (39) and depolarization induced by brain-derived neurotrophic factor in hippocampal neurons (40, 41) and SOCE in A431 human carcinoma A431 cells (42). It is thus clear that TRPC3 is involved in receptor induced Ca^{2+} influx in a variety of tissues. The native TRPC3 activity seems to mediate both store-operated and DAG sensitive modes of receptor dependent Ca^{2+} entry.

TRPC4 was the first TRPC channel implicated into a pathological condition. It is abundantly expressed in adrenal cells, where anti-sense TRPC4 suppresses both store depletion and IP_3 induced Ca^{2+} influx (43). Vascular endothelium of mice lacking TRPC4 demonstrate significantly decreased levels of receptor and store operated Ca^{2+} influx (44), which explain, in part, the impaired vasorelaxation which occurs in these animals (44). Similar deficits in Ca^{2+} signaling were observed in lung endothelial cells and thalamic neurons from TRPC4 deficient mice (45, 46), which results in decreased secretory events. The receptor dependent current in interstitial cells of Cajal resembles recombinant TRPC4; indeed, these cells express large amounts of TRPC4 (47). Further, TRPC4 siRNA suppressed Ca^{2+} influx in HEK 293 cells (13) and in human corneal cells (48). Inhibition of TRPC4 via anti-sense cDNA or TRPC4 antibodies also suppresses SOCE in mouse mesangial cells (49) and Ca^{2+} entry in smooth muscle cells respectively (50).

TRPC5 has been linked to rapid vesicle insertion in neurons, with suppression of native TRPC5 by a dominant negative mutant inhibiting neurite outgrowth (51). TRPC5 knockdown using siRNA inhibits SOCE in

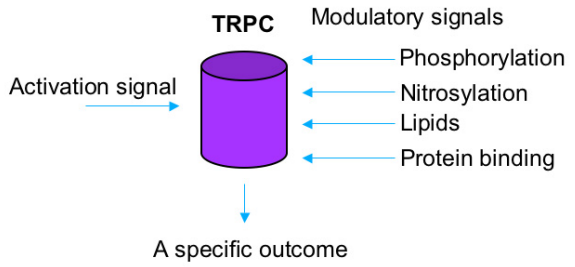

Figure 1. The integrative function of TRPC. All TRPC channels are under control from several signaling pathways. By integrating signaling inputs from these pathways, TRPC may vary the cellular response to stimulation depending on the environmental context or stimulation history.

human monocytes (52) and cholera toxin dependent Ca^{2+} influx in cultured neurons and neuronal cell lines (53). Further, TRPC5 pore mutants and TRPC5 antibodies suppress sphingosine-1-phosphate (S1P) and lyso-phosphocholine (LPC) induced smooth muscle motility and receptor dependent current (54, 55). Thus, native Trpc5 seems to be distinctly specific to a class of lipids.

Currents that resemble recombinant TRPC6 were detected in rabbit portal vein smooth muscle myocytes, which express very high levels of TRPC6 (56) and in cardiac myocytes (57); antisense driven TRPC6 suppression inhibited these currents (58). Similar results were obtained in pulmonary smooth muscle cells and prostate cancer epithelial cells where TRPC6 anti-sense also inhibits PDGF induced Ca^{2+} rise and cell proliferation (59, 60). This same approach also suppresses acetylcholine dependent current in PC12 cells (61). TRPC6 is also expressed at high-levels in human platelets where it contributes to thrombin induced Ca^{2+} influx (62). TRPC6 activity is also observed in A7r5 smooth muscle cell lines when stimulated by agonist DAG, with either activation being suppressed by anti TRPC6 siRNA (63). In the same cell type, dominant negative TRPC6 also suppresses Ca^{2+} influx (64). Further reports using this siRNA based approach reveal a major contribution of TRPC6 into bradykinin induced Ca^{2+} entry in vascular endothelial cells (38) and in RhoA activation and Ca^{2+} influx (65). Electrophysiological recordings in megacaryocytes also suggest a major role for TRPC6 in their Ca^{2+} signaling (66). Absolute majority of these studies point to DAG-dependent activation mode of native trpc6. TRPC6 was also shown to operate in tandem with Na^{+}/Ca^{2+} exchanger (64).

TRPC7 is implicated into receptor and store induced Ca^{2+} influx based on siRNA data (13), although this finding is disputed by the report from Muallem's and Worley's groups (67, 68). Anti-sense knock-down of TRPC7 also reveals a major contribution of TRPC7 in DAG-activated Ca^{2+} influx in human keratinocytes (69). Although TRPC7 was shown to operate both in store dependent and store independent modes under the recombinant conditions (70), receptor dependent but not store dependent Ca^{2+} influx was inhibited in DT40 cells by TRPC7 knockdown (71). The latter fact highlights the phenomenon previously observed with TRPC3 that behaved as a store operated channel when expressed at low levels and as a store independent channel when expressed at high levels (72). It is likely that such bimodal activation pattern reflects a need for coordination of the signaling molecules in plasma membrane and ER. Chapter 4 of the present review will discuss the molecular determinants of such interaction.

TRPC roles in other Ca^{2+} dependent cellular processes may also be inferred from pathological conditions associated with TRPC loss. Such conditions are surveyed in a recent review authored by one of us (73).

Taken together the discussed results clearly show that several TRPC types are involved in receptor and store dependent Ca^{2+} influx. It is clear that TRPC mediate Ca^{2+} responses in various tissues, triggered by various stimuli (Figure 1). Many of such stimuli activate several signaling cascades at the same time, and since TRPC multimerise, it is likely that the composition of the signaling complexes that TRPC reside in as well as the composition of TRPC multimers, dictates the exact activation profile of TRPC in different cells. Some of the major factors that regulate TRPC activity are discussed in the following chapter.

4. ACTIVATION MECHANISMS OF TRPC CHANNELS

4.1. Diacylglycerol

In 1999, Hofmann *et al* demonstrated that when exogenously expressed, TRPC 3,6, and 7 could be activated by analogues of DAG (74). Now more than eight years later, this result has been confirmed by tens of laboratories, yet the mechanism by which DAG induces channel activity has yet to be elucidated. Physiologically, DAG production for the activation of TRPC channels has been demonstrated to occur in multiple cell types, with IP_3 production being dispensable (75, 76) or contingent on TRPC expression levels (70, 77). Additionally, DAG activation of TRPC channels have been reported to be spatially localized in response to both agonist stimulation (78), and pharmacologically using Ca^{2+}-sensitive adenylyl cyclase as a reporter (79). Interestingly, PUFAs (which have a similar physical properties to DAG) are able to activate only *Drosophila* TRP channels, suggesting that fly TRPs may be quite distinct in their lipid regulation. To date, direct binding of DAG to any TRPC channel has yet to be reported, arguing that this interaction is not direct. Indeed, in our experiments using PIP-strips© with immobilized DAG, neither the N- nor C-terminus of TRPC3 conferred binding (van Rossum and Patterson *unpublished results)*. We suggest that perhaps the large body of literature demonstrating the role of DAG in neuronal vesicle fusion can provide answers to this problem. DAG is a known membrane-destabilizer due to its ability to flip between the inner and outer leaflets of the plasma membrane, which promotes vesicle fusion. This occurs due to the cone-shape of DAG, which allows for decreased membrane hydration while increasing the negative curvature of membranes and

maintaining a lamellar structure (80, 81). As TRPM7 has been proposed to have SNARE activity (82), this could also be true of TRPC channels, with DAG being the trigger for their fusion.

4.2. Activation in Response to Ca^{2+} store depletion

It has been hypothesized for more than ten years that TRPC channels comprise elements of store operated Ca^{2+} channels. Early reports from many groups demonstrated that essentially all exogenously expressed TRPCs can function as store operated Ca^{2+} channels in various cell culture model systems. The strongest evidence for TRP as store operated Ca^{2+} channels activity in endogenous systems is provided by a series of experiments in which various TRPC isoforms were knocked down using siRNA or antisense. Knockdown of all TRPC channels resulted suppressed native store operated Ca^{2+} influx (discussed in the previous chapter). More direct evidence for TRPC activity in store operated Ca^{2+} entry comes from the experiments with TRPC1. In multiple systems, particularly salivary gland cell lines (5, 11), transient knock-down of TRPC1 drastically alters SOCE. Further, TRPC1 heteromultimerization appears to impart Ca^{2+} store sensitivity to other TRPC members (13).

These results were difficult to interpret as with the few exceptions, these channels, when exogenously expressed, were able to recapitulate the I/V relationships observed in electrophysiological experiments on SOCE; further complicating this research is the heterogeneity of responses. In unpublished results of Patterson and Gill, even a HEK-293 cell line stably expressing TRPC3 can have store-operated or store-independent activity stochastically (i.e. some days it does and some days it doesn't), likely due to fluctuating expression levels. This notion is corroborated by the experiments in which TRPC3 expression levels were modulated using two different promoters. It was shown that TRPC3 sensitivity to store depletion is reciprocal to its expression levels. In the last few years, the major components of SOCE have been elucidated by the discovery of STIM and Orai functions (the putative ER Ca^{2+} sensor and a component of the store operated ion channel respectively) The seminal work in STIM/TRPC channels are from the Muallem and Worley groups (67, 68). They have demonstrated that STIM1, through its C-terminus, interacts directly with TRPC1, 4, and 5, imparting them with Ca^{2+} store sensitivity and allowing them to function as SOCs. They also demonstrate that TRPC3 and 6 can be co-opted as store operated channels through heteromultimerization with TRPC1, 4, or 5. These experiments further emphasize the importance of proper coordination of the interaction between endoplasmic reticulum and plasma membrane in TRPC activity (67, 68).

4.3. Mechanosensation

Gill and colleagues clearly demonstrate the mechanosensitive nature of TRPC6 (83). In a seminal paper, their electrophysiological studies demonstrate that TRPC6 can be activated by stretch, and that this mechanism is likely to be important for activation in response to receptor-stimulation as well. In experiments performed in HEK-293 and CHO cells with PLC inhibitors (to block possible stretch receptor activation), they observe TRPC6 activation due to osmotic pressure. The tarantula toxin GsMTx-4, a specific inhibitor of mechanosensitive channels by altering membrane-lipid/channel interactions, blocks TRPC6 activity (83). Further, this toxin blocks the activation of TRPC6 by either receptor or the direct application of DAG analogues. Whether TRPC6 heteromultimers, or other TRPC channels contain mechanosensitive properties remains to be determined. The physiological ramifications of this result are profound as TRPC6 is well established to have a role in smooth-muscle physiology, including vascular tone (56, 64). Mice deficient in TRPC6 have deficits in pulmonary vasoconstriction and alveolar gas exchange (84), thus understanding the full nature of the mechanosensitive nature of TRPC6 is likely to be important to our understanding of hypertension and pulmonary diseases.

5. TRPC MODULATION

One of the difficulties in studying the role of TRPC channels within biological processes is our poor understanding of their activation mechanism(s). It is clear that the activation of TRPC channels is polymodal, and can be influenced by phosphorylation, nitrosylation, glycosylation, protein-protein interactions, lipid interactions, mechanosensation, and Ca^{2+} store-depletion. Although evidence exists for all of these mechanisms, reconciling the results obtained with an exogenously expressed channel to responses observed with endogenous channels has proved to be challenging, in particular the activation of TRPC 3,6, and 7 by DAG. We present here a detailed description of these modulatory mechanisms for TRPC channels, and attempt to provide a coherent model by which all of these mechanisms may occur giving rise to specificity of activation in a cell-dependent manner.

5.1. Covalent Modifications

5.1.1. Phosphorylation

A number of phosphorylation sites have been documented for TRPC channels. In this section, we will address the studies that have drawn the most conclusive results; although, it is worth mentioning that in addition to kinases described here myosin light-chain kinase and calmodulin-dependent kinase II have been found to phosphorylate TRPCs (85, 86). Further, as no detailed phospho-peptide map has been performed for any of the TRPC channels, and multiple regions of these channels are serine/threonine rich, the work presented here likely only represents a fraction of the phosphorylation sites and/or kinases that can alter TRPC channel activity.

5.1.1.1. Protein Kinase C

Phosphorylation of TRPC channels by PKC has been demonstrated to occur in all members of the TRPC family in their C-termini (8, 87, 88) (Figure 2). Phosphorylation of these channels by PKC is strongly inhibitory to channel function. Perhaps best described is the regulation of TRPC6 by PKC by Kim *et al* (89). In this study, they identify Ser 768 in the TRPC6A isoform as the predominantly phosphorylated residue in response to muscarinic receptor stimulation. Through a detailed and

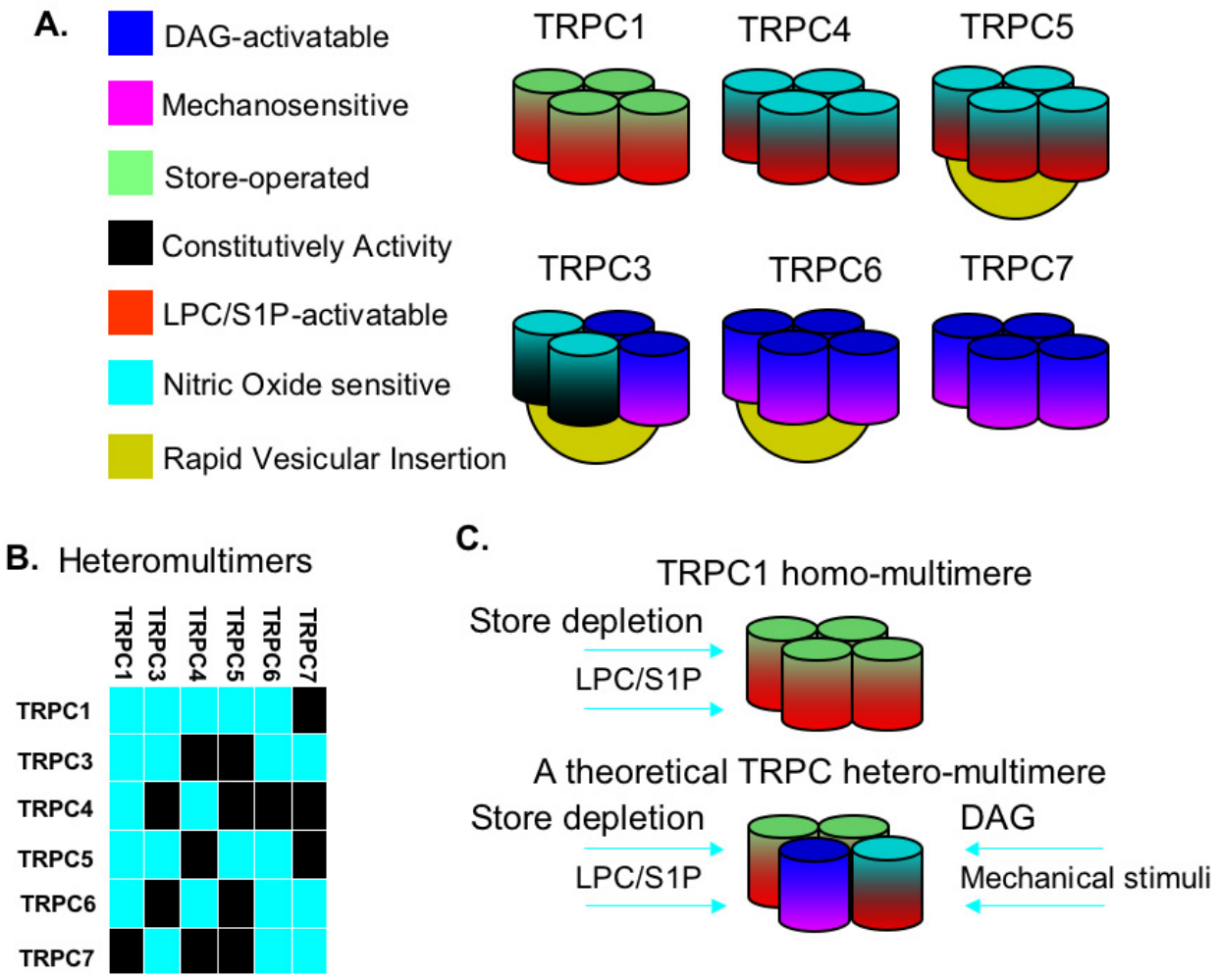

Figure 2. TRPC modulation and heteromultimerization. A. A summary of modulation mechanisms of TRPC. B. A network of TRPC multimerization as reported in (130). C. Theoretical consequences of TRPC multimerization. A repertoire of stimuli that modulate a TRPC channel could be significantly widened if subunits responding to various modalities are incorporated into one conducting unit.

rigorous biochemical study they determined that muscarinic receptor induced PKC phosphorylation of TRPC6 precipitates a protein-protein interaction complex including the muscarinic receptor, TRPC6, FKBP12, calceneurin, calmodulin, and PKC itself. In this process, activation of the muscarinic receptor leads to activation of TRPC6 either by DAG or IP_3. This activation is rapidly downregulated by the phosphorylation of TRPC6 by PKC, which induces the protein complex. Dephosphorylation of TRPC6 by calceneurin is drastically reduced if FKBP12 binding is blocked by its inhibitors FK506 or rapamycin. Further, FKBP12/calceneurin binding is necessary for the release of the muscarinic receptor from the complex, unlike PKC, which appears to only associate transiently during the phosphorylation process. This study demonstrates that through a series of phosphorylation/dephosphorylation cycles that the activity of TRPC6 could be fine-tuned. Although such detailed studies are lacking for the other TRPC channels, since all are inhibited by PKC, it seems likely that similar protein complexes likely regulate TRPC phosphorylation cycles to fine-tune their activity. Because PKC has a multitude of isoforms and regulators, as well as numerous phosphatases that can remove this covalent modification, this mechanism is well suited for adapting TRPC channel activity to perform cell-specific physiological processes.

5.1.1.2. Protein Kinase G

Phosphorylation of human TRPC3 by PKG is inhibitory to channel activity and occurs in the N-terminus (Thr-11 and Ser-263) (90, 91). These residues appear to be conserved in the other TRPC members, suggesting this regulation is likely to be universal. PKG phosphorylation of TRPC channels can be regulated by Ca^{2+}, nitric oxide, and PKC, all of which increase the catalytic activity of the enzyme. Initial studies by Yao and colleagues demonstrated that through mutation of these two residues in TRPC3, inhibition of the channel by NO donors (PKG activator), KT5823, DT3, or H8 (PKG inhibitors), or PMA (PKC activator) was relieved. This pharmacology was

consistent whether the channel was activated by store-depletion, OAG, or agonist suggesting that PKG impinges upon all forms of channel activation. It may be difficult to interpret the results of these studies using NO donors, as direct nitrosylation of TRPC channels has also been demonstrated.

5.1.1.3. Src-family tyrosine kinases

Early studies on store-operated and receptor-operated Ca^{2+} entry, shortly after the discovery of TRPC channels, identified a role for Src-family tyrosine kinases (STK) using pharmacological methods (92-94). It has now been determined that both TRPC4 and TRPC6 can be directly phosphorylated by STKs, with Fyn having the predominate activity. Odell *et al* clearly demonstrate that both endogenous and exogenous human TRPC4 activity in COS-7 and HEK-293 cells is increased upon tyrosine phosphorylation at Y959 and Y972 via STK in response to EGF stimulation (95). They also observe that TRPC4 levels are increased in the plasma-membrane after EGF-stimulation, but whether this is directly linked to its tyrosine phosphorylation remains to be determined. Further, their results also demonstrate that tyrosine-phophorylation allows TRPC4 and NHERF (a protein scaffold) to complex, reminiscent of PKC phosphorylation of TRPC6. Thus, it may be that TRPC phosphorylation is a key step in forming the multi-protein complexes that are observed with these channels (see protein-interaction). These results were mirrored by Mikoshiba's group who performed similar assays in COS-7 cells for TRPC6, although they did not identify the tyrosine residues which were phosphorylated (94). One important extension made in this study was the identification of the Fyn binding to the N-terminus of TRPC6. Assuming that TRPC4 and TRPC6 are phosphorylated at homologous positions, his suggests that the N-terminus of TRPC channels must be in very close proximity to the C-terminus. Indeed, the recent cryo-EM structure of TRPC3 clearly demonstrates that regions of the N-terminus must come in close contact with C-terminus of the channel in the closed configuration (96).

5.1.2. Nitrosylation

In a relatively recent report, Yoshida *et al* provide strong evidence for the direct nitrosylation of TRPC5 (97). Specifically, using multiple pharmacological methods for generating intracellular NO or hydrogen peroxide, both exogenously expressed and endogenous TRPC5 activity is rapidly increased upon their application, while extracellular NO was ineffective. Although TRPC5 was the only channel activated by relatively low levels of NO donor, TRPC3 could be activated at higher levels. In addition, co-expression of TRPC1 or 4 with TRPC5 allowed these channels to be gated by NO. Using site-directed mutagenesis, they isolated C553 and C558 in murine TRPC5 as the nitrosylation targets. These residues lie within the transmembrane regions of the channel itself, thus the authors propose that nitrosylation causes a structural change within these transmembrane helices which directly impact the channel pore structure, thus increasing ion-flux. Further, they determined that endogenous NO production from purinergic receptors in endothelial cells was sufficient to generate NO for TRPC5 activation. As endothelial cells are one of the major physiological targets of NO, this strongly suggests that TRPC5 is critical to their function. Multiple implications can be drawn from this study, with perhaps the most interesting being the possible role of anti-oxidants in the regulation of TRPC channel activity. Both NO and hydrogen peroxide can be generated in a variety of physiological and pathophysiological processes including receptor stimulation, heat shock, apoptosis, necrosis, and others, all of which are Ca^{2+} sensitive mechanisms. In cells possessing TRPC5, we hypothesize that the that the Ca^{2+} activity of TRPC5 is likely to impact some, if not all of the aforementioned processes. This seems reasonable to consider as intracellular anti-oxidants such as glutathione, vitamin C, and others would create a feed-back loop thereby regulating TRPC5 activity.

5.1.3. Glycosylation

All TRPC channels have glycosylation motifs, and therefore are likely glycosylated, although the functional role of this glycosylation still remains hazy. Perhaps the best description of TRPC glycosylation comes from the studies from Dietrich *et al* (98). They report that TRPC3 is mono-glycosylated while TRPC6 (a close relative) is di-glycosylated. Their results imply that di-glycosylated TRPCs are less likely to be constitutively active as when one of the glycosylation sites in TRPC6 is removed, it behaves similarly to TRPC3. TRPC3 tends to be constitutively active, in particular in overexpressing conditions, although when a second glycosylation site was introduced into the channel in the positions homologous to TRPC6, spontaneous channel activity was drastically reduced. Overall, these results suggest that glycosylation regulates the activity profile of TRPC channels, which could be further regulated by enzymes such as secreted glucuronidase, which has been demonstrated to regulate the activity of TRPV family members (99, 100).

5.2. Lipids

Although few lipid-binding domains have been identified within TRPC channels, it is well established that numerous lipids including DAG, polyunsaturated fatty acids (PUFAs), PIP_2, PIP_3, LPC, and S1P have been demonstrated to modulate their activity. We will discuss here the potential roles of each of these lipids in the regulation of TRPC channels, with special attention to the possible mechanisms that activate the DAG-sensitive TRPCs.

5.2.1. PIP_2 and PIP_3

Evidence for the regulation of TRPC channels by PIP_2 and PIP_3 has only been described in the last three years. Initial reports from Clapham and colleagues provided strong circumstantial evidence that rapid vesicular insertion of TRPC5 in hippocampal neurons was regulated by PIP_2, as PI5-kinase activity (which synthesizes PIP_2) was required for this process (51). Shortly thereafter, Tseng *et al* demonstrated that TRPC6 could associate with PIP_3, and that this association induced TRPC6 specific channel activity in both HEK-293 and Jurkat T-cells (101). Due to the lack of observable lipid-binding domains in TRPC channels by computational methods, elucidation of

these domains has been meager at best. It is worth noting that the TRP-box of TRPM4 (a common evolutionary feature in TRP channels C-terminal to the channel domain) has been demonstrated to bind PIP_2 (102, 103), thus this may also extend to TRPC channels.

In 2005, van Rossum *et al* described a "PH-like" lipid-binding domain in the N-terminus of TRPC3 that required interactions with a partial PH-domain in PLC□to bind PIP_2 (104). In this report, we demonstrated that a single point mutation (F43A) in TRPC3 inhibited PLC□ binding and the cell-surface expression of TRPC3. TRPC3 cell surface expression appears to be dependent upon this interaction with PLC□, and was confirmed by Caraveo *et al* (105). Some controversy has surrounded these reports as Zhang and colleagues performed a structural study using fragments of TRPC3 and determined that the fragments they used were unfolded structures not capable of binding to PLC□, thereby suggesting that our results were incorrect (106). They further hypothesize that that PLC□ binds to the C-terminus, rather than the N-terminus of TRPC3. In this study, they used the fragments that were used in our yeast-2-hybrid studies (residues 1-52) rather than the fragment that was used in our biochemical assays (1-171). This may explain the stark differences in our studies as the yeast-2-hybrid constructs are conjugated to □-galactosidase fragments, which could stabilize the structure of short fragments in the yeast system.

Most recently Montell and colleagues have isolated the PIP_3 binding site in the C-terminus of TRPC6 (107). In this report, they determine that residues 842-868 in TRPC6 bind to PIP_3 and that R853/K860 are key lipid-coordinating residues, and that this fragment can function as an intracellular PIP_3 "sponge", altering channel activity. Perhaps more interestingly, they demonstrate that this site is conserved in numerous ion-channels including TRPC1,5,7 as well as TRPV1, KCNQ1, and Ca_v 1.2. Thus, it seems likely that all TRPC channels bind to PIP_3 in the C-terminus and is likely important the regulation of the IP_3R, calmodulin, FKBP12, PKC, calceneurin, and other channel complex proteins in response to receptor stimulation.

5.2.2. Lysophosphatidic Choline and Sphingosine-1-Phosphate

To date, LPC and S1P have only been shown to regulate TRPC5 and heteromultimers containing TRPC5 (54, 55), although the N-terminus of TRPC3 has been demonstrated to bind to S1P in radioactive lipid-binding assays (104). Flemming and colleagues initially reported that activation of TRPC5 by intracellular LPC could occur both downstream and independently of G-protein coupled receptor signaling, suggesting that the lipid was acting directly on the channel similar to DAG stimulation of TRPC3/6/7 (55). Further, they demonstrated that this effect was specific for the headgroup and sidechains of the lipids, and not due to the generation of reactive oxygen species by the lipids tested. In a clever experiment, they used TritonX-100 to disrupt the plasma-membrane packing order and observe that unlike LPC, this inhibited TRPC5 activity, demonstrating that LPC is not increasing channel activity merely due to detergent effects. The physiological implications are that this would like TRPC5 directly to signaling pathways that activate phospholipase A_2, which is directly linked to immunological and vascular function. S1P has also been demonstrated by both intracellular and extracellular application to activate TRPC5 (54, 55). When applied to the surface of cells, S1P activates a G-protein coupled receptor pathway leading to activity, while when applied to the inner membrane using excised patches, S1P can directly activate TRP5. This strongly suggests that TRPC5 is an ionotropic receptor for S1P, and further suggests that investigation of this pathway may provide a means for determining the elusive role of S1P signaling in mammalian physiology.

5.2.3. Cholesterol

Two recent publications report similar findings on the effects of cholesterol on TRPC3 activity and Ca^{2+} entry in general. Graziani *et al* demonstrated that TRPC3 plasma-membrane levels are quite sensitive to the cholesterol content in the plasma-membrane, suggesting that pathophysiological effects due to increased cholesterol may involve increased levels of cell-surface TRPC3 (108). As TRPC3 has a high level of constitutive activity, this could have obvious effects on cell-cycle (atherosclerosis), and necrosis/apoptosis. Similarly Kannan *et al* demonstrated that increased levels of cholesterol in neutrophils increases TRPC1 levels in the plasma-membrane, as well as Ca^{2+} entry in response to receptor stimulation and Ca^{2+} store-depletion (109). These results suggest that membrane cholesterol content may also be important for immune cell inflammatory responses.

5.3. Interaction with auxiliary proteins.

As discussed above, several reports suggest that TRPC expression levels and perhaps composition of heteromultimers that form the ion channel likely modulates TRPC activation profile. One of the possible explanations for such behavior is that proper function of TRPC requires coordinated localization of plasma membrane and sub-membrane signaling machinery. Apparently, such coordination depends on scaffolding proteins. One of such proteins, STIM1 was discussed above and the discussion below will focus on other proteins that recently emerged as possible TRPC scaffolds.

5.3.1. Homer/IP_3R

The Homer family is comprised of by 3 genes that code for several multimodal products. The Homers were initially identified as immediate early gene products whose expression profile changes during long term potentiation and seizures (110). The Homer have common structure and, likely, similar mechanism of action (111). Homers contain an EVH domain that binds to proline rich sequences. The original Homer binding sequence decertified in Metabotropic glutamate receptors and IP_3 receptors is a proline rich sequence flanked by phenylalanine: PPXXF and PPXF (112). Homers' C-termini bear coiled coil and leucin zipper domains, which are responsible for dimerization and, perhaps, multimerization. Such sequences are absent in short forms of Homer. While dimerization of full length Homers brings

together various elements of Ca^{2+} signaling complexes, the short forms play the opposite role as they unbind the molecules that associate due to interaction with the full length Homers (111, 113, 114). In neurons, the short forms of Homer physically unbind metabotropic glutamate receptor and IP_3R and significantly retard signal transduction between these molecules (115).

The binding of Homers to TRPC was shown by Muallem and Worley's groups that demonstrated selective association of Homer 1 with a select subset of TRPC channels. Mutations that abolish TRPC binding to Homer and short forms of Homer affected TRPC interaction with IP_3R and resulted in spontaneous channel activity (116).

The TRPC/Homer/IP_3R binding seems to have an effect on TRPC targeting to the plasma membrane as well. TRPC3, also becomes spontaneously active if hot bound to IP3R through Homer (117). Severing of TRPC3/Homer/IP_3R link resulted in abnormally high TRPC3 levels in the plasma membrane under the resting conditions. These findings indicate that TRPC3/IP_3R coordination is necessary for the proper insertion of TRPC3 into plasma membrane in response to stimulation.

It is unknown at present whether the Homer levels change in nonexcitable cells as a result of stimulation. Although it is clear that Homer finetunes TRPC dependent Ca^{2+} signaling, the dynamic range of such Homers' activity requires further investigation.

As discussed above, the apparent dependence of TRPC activation mode on the levels of expression can be explained by a requirement of coordinated expression and localization of the membrane and sub-membrane elements of Ca^{2+} signaling complexes. One of such TRPC partners in the Ca^{2+} signaling complexes is IP_3R. It is well established that all TRPC physically interact with IP_3R (116). The binding seems to be dynamic and regulated by Homer (116), Junctate, and calmodulin (see below). The functional significance of such interaction has not been settled. While some data show that binding to IP_3R can activate TRPC (118, 119) and that the regions of IP_3R that bind TRPC3 have a dominant negative effect on Ca^{2+} entry (120), others show that IP_3R is not required for TRPC activation by receptor stimulation (75, 76). It is likely that Homers (or, perhaps, Junctate) coordinate TRPC and IP_3R interaction, which may explain variability of the reports on IP_3R dependence of TRPC activation.

5.3.2. Calmodulin

Although calmodulin is not typically thought of as a scaffolding protein, calmodulin can heavily impact the ability of proteins to complex. Further, calmodulin can act as a "shuttle" moving proteins between membranes (121) Haeseler F, BBRC 2002). Zhu and colleagues were the first to discover the calmodulin binding site in TRPC3 (122, 123) where they reported that calmodulin inhibits to channel activity; a result which could be due to improper channel localization (124). Calmodulin is now well established to bind to the C-terminus of TRPC channels (amino-acids 842-868 in TRPC6), and shares this binding site with both the IP_3R and PIP_3 (122-124). As discussed previously, calmodulin is also critical for formation of the PKC/FKBP12/calceneurin complex with TRPC6. Due to calmodulin's ability to apply physical force to proteins it associates with in the Ca^{2+} bound state, it stands to reason that calmodulin could significantly distort the structure of TRPC channels, thus exposing protein binding sites which are not accessible in the absence of calmodulin. Whether there are additional calmodulin binding sites in TRPC channels (which seems likely) remains to be determined.

5.3.3. Junctate

The evidence for the role of Junctate in regulation of TRPC activity comes from experiments with TRPC3 and TRPC2 reported in COS-7, HEK 293 cells and rodent sperm (125, 126). It was shown that this endoplasmic reticulum resident protein binds IP_3R via its C terminus, which also has putative Ca^{2+} binding sites (126). The N terminus of Junctate binds to TRPC channels to form a macromolecular complex with IP3R and TRPC whose disruption affects activation of TRPC3 and TRPC2 (125, 126). It is thus possible that Junctate also participates in coordination of molecules in the plasma membrane and endoplasmic reticulum. Junctate and IP_3R bind to different sites in trpc2. Interestingly, DAG did not promote acrosome reaction in these studies even through TRPC2 channels appeared to be functional (125). Much like it is the case with Homer, it is unclear whether Junctate expression changes with cell stimulation and thus the dynamic aspects of the Junctate role in TRPC regulation cannot be inferred at this moment.

6. TRPOTHESIZING

A wealth of information towards understanding the role of TRPC channels in physiology has been collected in the last twelve years; yet, in most cases, how they exert their function within cells and the mechanism(s) by which it is regulated remains to be determined. Therefore, we provide here a "TRPothesis" how the basic properties of TRPC channels are likely to provide cells with a mechanism for "tailoring" their Ca^{2+} entry pathways to elicit cell-specific developmental and signaling pathways. These ideas could be extended to the multitude of cellular processes TRPC channels have been linked to (neurite outgrowth and development, immune cell responses, sensory perception, etc).

For example, the regulation of vascular smooth-muscle tone is under the control of nitric oxide released from endothelial cells (127). Endothelial cells express high levels of TRPC5, which is activated by nitric oxide (see above). As endothelial cells contain Ca^{2+} sensitive isoforms of nitric-oxide synthase, we hypothesize that nitric oxide production works to increase intracellular Ca^{2+} via TRPC5 in a feed-forward cycle. Heteromulitmers of TRPC5 with other TRPC channels would allow this signaling loop to have multiple properties. For example, TRPC3/5 heteromultimers could provide even more Ca^{2+} entry as TRPC3 is generally constitively active and nitric-oxide sensitive. TRPC5/6 heteromultimers might allow for endothelial cells to feel stretch in the vasculature, thus

synchronizing the endothelial cells with the contractions they are contributing to. Once released into the fluids surrounding the endothelial cells, nitric oxide enters smooth muscle cells, which also contain multiple TRPC channels, including mechanosensitive TRPC6, which activates in response to muscle contraction (128). Indeed, nitric oxide has been demonstrated to rapidly rapidly potentiates Ca levels in smooth muscle which alters contraction (128, 129). This increase in intracellular Ca^{2+} could stimulate rapid vesicle fusion via TRPC3/6 or TRPC5/6 heteromultimers, allowing for NO regulation of smooth-muscle Ca^{2+} as well. One could even envision that TRPC6 homomultimers provide Ca^{2+} signals for the regulation of contraction, while other TRPC currents regulate cell growth and maintanence. This makes sense in considering atherosclerosis, a poly-genetic disease which is directly linked to alterations in Ca^{2+} signaling.

7. SUMMARY

The data surveyed in this review show that TRPC channels are involved in converting a variety of signaling inputs into Ca^{2+} influx. It appears that I addition to the main activation signal, TRPC isoforms are also under control from other signaling inputs such as covalent modification, or interaction with lipids and auxiliary proteins. One can suggest that it is due to this polymodal regulation and multimerization of different TRPC isoforms that TRPC channels can integrate several signaling pathway and specifically finetune their activity to the immediate need of the given cell or environment.

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Send correspondence to: Kirill Kiselyov, 519 Langley Hall, 4249 Fifth Avenue, Pittsburgh, PA 15260, Tel: 412-624-4317, Fax: 412-624-4759, E-mail: kiselyov@pitt.edu

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