Review

TRPC3/6/7

Topical aspects of biophysics and pathophysiology

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Nonselective and lipid-regulated cation channels formed by TRPC3, TRPC6 and TRPC7 have recently obtained attention in view of their potential pathophysiologival impact. It appears as a particular challenge to understand the molecular basis of TRPC3/6/7-related diseases in order to further delineate their value as therapeutic targets. The multifunctional nature of these channel proteins, based on a complex, versatile heteromerization potential along with highly promiscuous gating and mixed cation permeation properties, make these channels pivotal players in cellular signaling networks. Here we summarize newsworthy aspects of TRPC3/6/7 physiology and pathophysiology that open the view on novel therapeutic strategies based on these TRPCs as target structures.

Introduction

Since the very beginning of research on mammalian trp homologs with the discovery of human TRPC3 as one of the closer relatives of the Drosophila trp gene product,\(^1\) this membrane protein as well as its closer human relatives TRPC6 and TRPC7 are considered to play a significant role in Ca\(^{2+}\) homeostasis of a wide range of human tissues, and more recently these signaling molecules have been implicated in a variety of diseases ranging from kidney disease, over Alzheimer’s disease to heart failure.

These three mammalian, hexaspan membrane proteins give rise to nonselective cation conductances when overexpressed in standard expression systems\(^2-4\) and are unequivocally activated by stimuli generated in response to enhanced cellular phospholipase C activity (reviewed in refs. 5 and 6). Specifically the lipid mediator diacylglycerol has been identified as a prominent input signal that controls the activity of TRPC3/6/7 channels.\(^7\) Nonetheless, other mechanisms of channel regulation including sensitivity to Ca\(^{2+}\) store depletion, mechanical stress and redox-dependent alterations in membrane lipids have been suggested (reviewed in refs. 5 and 8). Moreover, evidence for divergent regulatory gating properties depending on the composition of heteromeric TRPC3 channel complexes has been hypothesized.\(^9-12\) Thus, TRPC3/6/7 channels have emerged as a family of cation channels that serve as versatile downstream effectors for a wide range of hormone and neurotransmitter receptors and that are, in addition, tightly linked to various aspects of cellular homeostasis. Consequently, TRPC3/6 and 7 related cation channels are generally considered as a prototypical family of “receptor operated channels”. The unique properties of these TRPC proteins as integrating sensor molecules that are able to translate a dazzling array of input stimuli into distinct pattern of cellular Ca\(^{2+}\) signals to govern specific cellular function such as gene expression, contraction, proliferation and apoptosis impressively foreshadow the role of these proteins in Physiology and Pathophysiology. As a mechanistic basis of TRPC channel-related diseases, mutations in a TRPC gene, altered expression as well as pathological gating processes may be considered. Direct experimental evidence for a role of TRPC3/6/7 in the pathogenesis of systemic diseases has indeed recently been obtained and is outlined and discussed below.

TRPC3/6/7 and Neurological Disorders

TRPC channels are widely expressed in central nervous system,\(^13\) pointing to a potential role of these channels in Neurophysiology and neurological disorders. As a typical example, TRPC6 is expressed in the molecular layer of the dentate gyrus of the hippocampus,\(^14\) a brain region considered to play a crucial role in associative memory. Along these lines, a pathophysiologival impact was indicated by the observed crosstalk between TRPC6 and mutated forms of presenilin2, which may be linked to the onset and progression of Alzheimer’s disease. In HEK293 cells, co-expression of TRPC6 with a pathophysiologically relevant mutation of presenilin2 resulted in abolished agonist-induced TRPC6 activation and consequently altered Ca\(^{2+}\) entry.\(^15\)

TRPC3 channels were suggested to mediate brain-derived neurotrophic factor (BDNF)-dependent dendritic remodelling\(^16\) in the hippocampus. BDNF-induced Ca\(^{2+}\) elevations were reported to be TRPC3 dependent, and strikingly, the growth factor-induced membrane current (\(I_{\text{BDNF}}\)) was absent after TRPC3 knockdown using small interfering RNA. In cerebellar granule neurons (CGNs), both TRPC3 and TRPC6 were recently demonstrated to confer protection against serum deprivation-induced cell death and, thus, appear important for neuronal survival.\(^17\) Notably, the importance of TRPC3 in neuronal growth was recently emphasized also by a proteomic study that revealed a physical link between TRPC3 and
proteins involved in neuronal growth. A similar conclusion was reached for TRPC6 in a study that identified TRPC6 as a molecular target of hyperforin, a bicyclic polyphenylated acylphloroglucinol derivate with antidepressive effects. Hyperforin was shown to induce neuronal axonal sprouting that was strictly TRPC6 dependent.

Importantly, there is some evidence for a role of TRPC channels in cell fate, differentiation and survival. Such native channels are likely comprised of heteromeric pore structures. Evidence for a specific link between TRPC3 and the development of a recessive neuromotor disease was recently obtained in a mouse model that lacks TRPC3 expression. Homozygous Δ202 transgenic mice carry a SV40 T transgene that is inserted in the trpc3 promoter region and blocks TRPC3 transcription and TRPC3 channel expression which results in paralysis in the hind limbs and atrophy.

**TRPC3/6/7 and Cardiovascular Disorders**

In the cardiovascular system virtually all TRPC isoforms are expressed and a link between TRPC channel complexes and proliferative, hypertrophic processes, as well as processes that determine excitability of vascular smooth muscle and myocardium has recently been demonstrated. A role of TRPC3/6/7 was uncovered in transgenic mice overexpressing either TRPC isoform in the heart. In particular, TRPC6 overexpressor mice develop a severe cardiac hypertrophy in early stages of life. Similarly, TRPC3 overexpressor mice are prone to develop hypertrophy and cardiomyopathy after pressure overload. TRPC7 might contribute to pathogenesis of heart failure, as apoptosis and TRPC7 expression are concomitantly increased in the failing myocardium of Dahl salt-sensitive rats. In this system TRPC7 may act as a mediator linking AT1-activation to myocardial apoptosis via calcineurin activation. Consistently, TRPC3 was found to contribute to increased apoptosis in cardiac myocytes subjected to ischemia/reperfusion. It is important to note that channels formed by these two TRPC species in contrast to TRPC6 channels, were found to display significant basal channel activity and might determine basal Ca2+ homeostasis, which may be considered as a link to apoptosis. Several studies indicated that hypertrophic progression involves a functional interaction between TRPC proteins and proteins of the calcineurin/NFAT pathway that requires sustained Ca2+ entry for activation. A TRPC3/6/7 mediated Ca2+ entry, triggered by stimulation of the GPCR pathway, may activate the Ca2+-dependent phosphatase calcineurin that in turn dephosphorylates the transcription factor, nuclear factor of activated T cells (NFAT) which translocates into the nucleus and regulates transcription of hypertrophic genes. Importantly, such events may take place in certain microdomains in cardiac myocytes that are spatially segregated from Ca2+ signals that regulate contraction. In rat neonatal cardiac myocytes, for example, TRPC3 showed a cellular distribution distinctly different from that of the L-type Ca2+ channel, Cav1.2. On the other hand, another recent study suggests that activation or even basal activity of TRPC3/6 channels results in significant membrane depolarization to affect Cav1.2. This chain of events may well generate altered excitation-contraction-cycling in the heart and enhanced arrhythmogenesis. Such pathological mechanisms may well involve the cardiac Na/Ca exchanger as this transport system has been identified as an important signaling partner of TRPC3 in the rat heart, and of TRPC6 in smooth muscle. In this context, another interesting finding is the observation of a store-operated Ca2+ entry in pacemaker cells of the mouse sinoatrial node, which may be attributable to TRPC channels expressed in this part of the heart (TRPC1,2,4-7) and may regulate pacemaker activity.

High TRPC6 expression is typically found in blood vessels, as exemplified for the pulmonary system. Here, overexpression of TRPC6 has been linked to idiopathic pulmonary arterial hypertension (IPAH), a fatal disease characterized by excessive, Ca2+-dependent smooth muscle cell proliferation. TRPC6 together with other TRPC isoforms might be involved in the development of hypoxic pulmonary vasoconstriction. Interestingly, TRPC6 was found to mediate membrane depolarization and vasoconstriction induced by elevated intravascular pressure in the vascular smooth muscle. This phenomenon indicates some mechanosensitivity of TRPC channels. However, a more recent heterologous expression study argues against direct mechanosensation by TRPC channels and indicates that the effects observed in native tissues are due to indirect mechanisms such as mechanosensitivity of phospholipase C activity. Paradoxically, mice display an elevated blood pressure and increased agonist-induced contractility of aortic rings and cerebral arteries. As the basis of this phenotype, TRPC3 was found upregulated in smooth muscle of mice. Replacement of TRPC6 dominated heteromers by TRPC3 channels may well result in a constitutively active cation conductance and consequently in more depolarized membrane potentials. Thus, TRPC3 could be a key player in generation and progression of hypertension which is also supported by the finding of increased TRPC3 expression in monocytes from spontaneously hypertensive rats.

TRPC family members have been suggested as functional receptor-operated cation channels as well as SOCs in another important cell type of the cardiovascular system, the endothelium. Systemic knock-out of TRPC4 mice was reported to impaired store-operated Ca2+ entry in the endothelium. As one prominent consequence, endothelial permeability was affected by deletion of TRC4, suggesting a role in inflammatory processes. Nonetheless, endothelial barrier function might also be controlled by TRPC6 as well as TRPC3, as these species may well form heteromers with TRPC1 and/or TRPC4. In human pulmonary endothelial cells, TRPC6 deletion significantly reduced Ca2+ entry, prevented RhoA activation and inter-endothelial junctional gap formation after thrombin stimulation. Oxidant stress is well known to increase vascular endothelial permeability and to promote leukocyte adhesion. TRPC3 was identified as the basis of the redox-activated cation conductance, which was recently shown to heteromultimerize to a redox-sensitive TRPC3-TRPC4 channel complex in porcine aortic endothelial cells. The exact pathophysiological role of TRPC3/6/7 in the endothelium has so far not been clearly delineated.

**Other Potential Links between TRPC3/6/7 and Disease**

Similar to the heart, TRPC channels, in particular TRPC3, were found as important regulators of the calcineurin-NFAT signaling pathway in skeletal muscle and may thus be implicated in muscular disorders. The exact TRPC composition of these channels linked to NFAT signaling is unclear. Repeated neuromuscular stimulation results in a conversion from fast into slow skeletal muscle through a calcineurin-dependent mechanism, which may involve TRPC3 mediated Ca2+ entry.
Ca²⁺ entry, a defect that was rescued by transfection with wild type therapeutic targets (Fig. 1). Still missing and appears as a key step to establishment of TRPC as a functional role of TRPC structures and protein interactions and their potential interplay and impact in physiology/pathophysiology as outlined for TRPC3. Ion permeation and gating of TRPC channels are governed by multimeric, potentially heteromeric, assembly of the pore complex as well as by protein-protein interactions that generate specific regulatory properties such as composite ligand/lipid binding or targeting domains (e.g., PI, Phosphoinositides). The distinct properties of a TRPC channel complex along with its specific ability to communicate with input receptors or effector signaling molecules (e.g., NCX, Sodium calcium exchanger and/or CaV, voltage-gated Ca²⁺ channels) determines its role in physiology and pathophysiology.

Genetic analyses of families affected with the autosomal dominant disorder of focal and segmental glomerulosclerosis (FSGS), which is characterized by a loss of the integrity of the glomerular filter, have revealed a TRP channelopathy based on mutations of the trpc6 gene on chromosome 11q. Two of the TRPC6 mutations have been linked to an increase in Ca²⁺ transients in podocytes which has been suggested to affect structural proteins maintaining the filtration barrier as well as to PLC dependent processes resulting in podocyte apoptosis.

In T lymphocytes, truncated mutants of TRPC3 have been identified that generate a defect in Ca²⁺ homestasis, specifically in Ca²⁺ entry, a defect that was rescued by transfection with wild type TRPC3. This observation in view of the discovery of ORAI as the principle molecular basis of the CRAC Ca²⁺ entry pathway in immune cells and recent reports indicating the ability of TRPCs to form heteromeric complexes with ORAI proteins, as established for K⁺ channels, have revealed a TRP channelopathy based on mutations of the trpc6 gene on chromosome 11q. Two of the TRPC6 mutations have been linked to an increase in Ca²⁺ transients in podocytes which has been suggested to affect structural proteins maintaining the filtration barrier as well as to PLC dependent processes resulting in podocyte apoptosis.

Nonetheless, gating of the channels formed by TRPC3/6/7 proteins still remain highly enigmatic and detailed knowledge on the three dimensional architecture of the permeation pathway as well as gating structures of these TRPCs are sparse or even lacking. Moreover, these key functional structures are likely determined in a critical manner by additional interaction partners such as pore forming heteromerization partners as well as ancillary subunits that may vary between cell types and give rise to an array of native TRPC3/6/7 channel complexes that serve highly specific functions in cellular signaling. It is now an obvious challenge to delineate the precise composition of the native TRPC3/6/7 complexes that are involved in a particular pathological situation. Detailed knowledge on the protein-protein interactions within pathophysiologically relevant TRPC3/6/7 signalplexes may enable the design of novel strategies for selective interference and therapeutic intervention. An overview on the candidate interaction partners and their potential role in TRPC3/6/7 physiology and pathophysiology is given in Figure 1 and outlined below.

Figure 1. Functional role of TRPC structures and protein interactions and their potential interplay and impact in physiology/pathophysiology as outlined for TRPC3. Ion permeation and gating of TRPC channels are governed by multimeric, potentially heteromeric, assembly of the pore complex as well as by protein-protein interactions that generate specific regulatory properties such as composite ligand/lipid binding or targeting domains (e.g., PI, Phosphoinositides). The distinct properties of a TRPC channel complex along with its specific ability to communicate with input receptors or effector signaling molecules (e.g., NCX, Sodium calcium exchanger and/or CaV, voltage-gated Ca²⁺ channels) determines its role in physiology and pathophysiology.

Biophysical and Molecular Basis of the Pathophysiological Role of TRPC3/6/7

The suggested role of TRPC channels as critical or even indispensable determinants of physiological functions and as key players in pathological processes is based on rather unique biophysical and regulatory properties. Ion permeation and gating properties of channel complexes formed by a particular TRPC protein determine its Physiological and Pathophysiological role (Fig. 1). These properties of native TRPC complexes are created by a highly variable, multimeric pore assembly and the interaction of pore forming TRPC subunits with regulatory and ancillary subunits. Notably, the exact structural basis of the two hallmark features of TRPC3/6/7 channels, i.e., nonselective cation permeation and lipid dependent activation/gating, have so far not been uncovered. Functional domains involved in these properties have convincingly been assigned both by bioinformatics/analog approaches as well as by mutational analysis. In this context, the concept of an ion permeation pathway being formed by the linker between transmembrane segments 5 and 6 of six-transmembrane cation channel proteins, as established for K⁺ channels, has received some confirmatory evidence by mutations in a LFW motif within the putative pore (P) domain that abolished channel function. Lipid sensitive motifs and structures related to the targeting of TRPC channels into specific lipid microdomains have been localized in the N- as well as C-termini of the proteins (Fig. 1), suggesting these cytoplasmic domain as essential determinants of lipid regulation in terms of lipid-dependent recruitment and/or gating. A novel mechanism for TRPC6 channel regulation that integrates channel regulation by PIP₃ and Ca²⁺/CaM has recently been suggested. A phosphoinositides (PI)- binding site was found in the C-terminus of TRPC6 at aa 842–868 overlapping with the CIRB region (aa 838–872). Mutations of this specific site, that increase the potency of PIP₃ to interact with TRPC6, resulted in an enhanced TRPC6 current due to a disruption of the TRPC6-CaM interaction. Nonetheless, gating of the channels formed by TRPC3/6/7 proteins still remain highly enigmatic and detailed knowledge on the three dimensional architecture of the permeation pathway as well as gating structures of these TRPCs are sparse or even lacking. Moreover, these key functional structures are likely determined in a critical manner by additional interaction partners such as pore forming heteromerization partners as well as ancillary subunits that may vary between cell types and give rise to an array of native TRPC3/6/7 channel complexes that serve highly specific functions in cellular signaling. It is now an obvious challenge to delineate the precise composition of the native TRPC3/6/7 complexes that are involved in a particular pathological situation. Detailed knowledge on the protein-protein interactions within pathophysiologically relevant TRPC3/6/7 signalplexes may enable the design of novel strategies for selective interference and therapeutic intervention. An overview on the candidate interaction partners and their potential role in TRPC3/6/7 physiology and pathophysiology is given in Figure 1 and outlined below.
Pore-Forming Interactions

Native TRPC channels are likely comprised of a heteromeric ensemble of pore forming subunits as numerous compositions of TRPC heteromers appear possible and expression of multiple TRPC species has been demonstrated for most tissues investigated so far. Although heteromor- phizations in expression systems suggested that pore complexes are formed preferentially by members of a subfamily (TRPC3/6/7),49 more heterogeneous compositions of pore complexes in native tissues have repeatedly been demonstrated.21,51–53 Thus, a variety of native pore complexes with divergent biophysical characteristics may exist for a particular TRPC isoform. Heteromeric assembly may determine ion permeation, regulation and gating as well as cellular targeting of the channels (Fig. 1). Ion permeation may, to some extent, vary in TRPC3/6/7 heteromers of different stoichiometry as expected from moderate differences in permeation properties of homomeric channels in classical overexpression experiments yielding pCa/pNa values within the range of 1.6–5. Nonetheless, other potential protein partners that may affect the permeation properties in more profound manner have emerged and may be considered for particular cell types. Others and we have previously obtained evidence for inter-subfamily heteromor- phization of TRPCs, demonstrating interaction as well as generation of specific pore properties. Potential pore-forming partners of TRPC3 may be TRPC1 and TRPC4/5 (reviewed in ref. 5). Such heteromers may well exist in particular tissues and exhibit atypical permeation properties. More recently, evidence for an interaction of TRPC3 and TRPC6 with store-operated membrane proteins of the ORAI family have recently been reported.11,12 Assembly of these two different types of membrane proteins, which are both able to generate cation permeation pathways on their own, has been shown to generate store-operated Ca2+ entry pathways of distinct properties upon heterologous coexpression. Heteromeric pore complexes with unique features including distinct cation selectivity and gating appear possible and may well be involved in pathological processes. Importantly, heteromeric TRPC pore structures are indeed likely to exhibit distinct gating features as even closer relatives, such as TRPC3 and TRPC6 were demonstrated to generate channels of divergent properties upon heterologous overexpression.9

Interactions that Determine Targeting, Receptor-Dependent Regulation and/or Gating

A large array of proteins that appear tightly involved in TRPC channel function and/or regulation have been identified and structural motifs in TRPC channels that are responsible for interaction with such regulatory partners or channel subunits have been identified (reviewed in ref. 54). TRPC3,6,7 contain a highly conserved CaM-and IP3R-binding site, (CIRB,55 and a coiled-coil domain in the C terminus (Fig. 1). The CIRB region (aa 761–795) has been postulated to determine activation/inactivation of TRPC3. In terms of a conformational-coupling model, the activated IP3R has been suggested to displace CaM from CIRB representing a crucial step in activation of TRPC3 channels.56 Alternatively, the CIRB region appears essential for a correct channel targeting of TRPC3 to the plasma membrane.57 The C-terminus of TRPC3 may also be crucial for binding junctate, an integral calcium binding protein of endo(sarco)plasmic reticulum membrane. The interplay between TRPC3-IP3R apparently requires junctate, since knock down of junctate was found to result in reduced agonist-activated calcium release from intracellular stores and calcium entry via TRPC3.58,59 With the discovery of STIM1 as an ER resident Ca2+ binding protein that regulates SOCE,60–64 which as suggested indirectly affects TRPC channels to enable store dependent regulation of TRP-related channels,65 the mechanisms of TRPC activation may be expanded. According to more recent findings, STIM seems to regulate TRPC1 activity, and possibly in concert with ORAI also TRPC3.11,12

Since TRPC channels exhibit a CaM binding domain it may become obvious that there may also be an indirect interaction with the Ca2+/CaM-regulated phosphatase calcineurin. TRPC3 and TRPC6 have been shown to regulate the calcineurin/NFAT pathway as a crucial mechanism in the progression of muscle hypertrophy (see above). In neuronal cells, a vice versa mechanism may take place with TRPC6 as a target of calcineurin-dependent dephosphorylation. TRPC6 associates with the Ca2+/CaM-regulated phosphatase calcineurin, to form a multiprotein complex, together with M1 muscarinic acetylcholine receptors (mAChRs), PKC and the immunophilin FKBP12. It has been suggested, that PKC medi- ated phosphorylation of TRPC6 triggers an interaction between FKBP12 and TRPC6 which results in a recruitment of calcineurin/calmodulin that in turn dephosphorylates TRPC6 releasing M1 mAChRs from TRPC6 channels.66 Immunophilin binding motifs are as well present in TRPC3 and TRPC7 represented as LP dipeptides located in the C-terminal proline rich sequence.67 It will be an important task to investigate the functional interactions between TRPC channels, calmodulin-calcineurin and immunophilins in order to advance the knowledge on molecular processes that are involved in calcineurin/NFAT dependent cardiac hypertrophic progression, skeletal muscle adaptation, as well as differentiation and proliferation of immune cells.

Interactions that Govern Dynamic Membrane Recruitment

Rapid insertion and retrieval of channel complexes in the plasma membrane has been suggested as a potential process involved in the regulation of TRPC conductances. Vesicular trafficking has been shown to involve association of TRPC proteins with an array of vesicle targeted proteins. TRPC3 channels, for example, reside in a population of mobile, sub-plasmalemmal vesicles, from which the protein is delivered towards the plasma membrane during GPCR stimulation. A variety of SNARE proteins such as syntaxin, SNAP23 and NSF were found to co-localize with TRPC3 channels in the HEK293 expression system, and endogenous neuronal TRPC3 was co-immunoprecipitated with both VAMP2 and syntaxin.38 A putative VAMP2 interaction motif was found in the N-terminus of TRPC3. TRPC6 activation may involve the synaptic vesicle-associated protein, snapin, that links the α1A-adrenoceptor with TRPC6 in neuronal PC12 cells. Upon α1A-adrenoceptor activation the pre-formed snapin-α1A-adrenoceptor dimer recruits TRPC6 to form a triple complex by facilitating the insertion of TRPC6 into the plasma membrane which results in an increased Ca2+ entry.69 RNF24 has been suggested more recently as another potential interaction partner of TRPC channels that determines cellular trafficking.70 Translocation and retrieval of TRPC channels from the plasma membrane may also be regulated by Homer proteins. TRPC3 channels may exist as TRPC3-Homer (H1)-IP3Rs complexes under resting conditions and
it has been suggested that upon receptor stimulation, IP_3 binds to the IP3Rs to release Ca^{2+} from the stores and to dissociate between IP3Rs and H1 to form a IP3Rs-TRPC3-Homer complex which translocates to the plasma membrane. 

Apart from regulatory subunits, the lipid environment of TRPC channel complexes in the plasma membrane itself appears to exert a profound impact on TRPC-mediated Ca^{2+} signaling. TRPC channels have been identified as components of signalplexes that reside in distinct plasma membrane lipid domains, named lipid raft domains, or caveolae. Consistently, a putative caveolin binding domain in the cytoplasmic N termini of TRPCs was identified. This domain is expected to associate with the lipid-binding scaffold caveolin, an interaction that is likely involved in cellular targeting and regulation of the channels. Moreover, TRPC3 was found to associate via its N terminus with phospholipase C (PLC) γ1 to form a bimolecular PH domain, which binds PIP_2 as well as sphingosine-1-phosphate. This unique domain was demonstrated to govern plasma membrane targeting and function of TRPC3 channel complexes.

Crosstalk with Signaling Partners and Specificity of TRPC3/6/7 Signaling

The generation of a highly specific pattern of Ca^{2+}, as well as electrical signals by a particular TRPC complex is not only the result of the permeation and gating properties of the pore complex but involves also its ability to communicate with a particular set of input signaling pathways (e.g., receptors) as well as signaling effectors such as other channels or transporters. In exitable tissue, both voltage-gated Ca^{2+} channels as well as NCX1 was suggested to contribute to TRPC signalling. The communication with these signaling partners is likely governed by targeting and trafficking processes as outlined above. It appears important to note that such crosstalk with other electronegic transport systems is expected to determine the signal output of a given supramolecular TRPC complex both in terms of spatial and temporal Ca^{2+} signaling as well as in terms of modulation of excitability and electrical properties of neuronal and muscle tissues.

Conclusion and Perspective

TRPC3/6/7 proteins function as pore forming subunits within large macromolecular signaling assemblies, of which some may play a pivotal role in human pathophysiology. Regulatory subunits of such TRPC complexes and specific protein-protein as well as protein-lipid interactions may be considered as attractive target sites for future therapeutic intervention. A key step towards the development of such therapeutic strategies will be the elucidation of the molecular composition of native and pathophysiologically relevant TRPC complexes.

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