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Review

Cytoskeletal and scaffolding proteins as structural and functional determinants of TRP channels☆

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ABSTRACT

Transient receptor potential (TRP) channels are six transmembrane-spanning proteins, with variable selectivity for cations, that play a relevant role in intracellular Ca^{2+} homeostasis. There is a large body of evidence that shows association of TRP channels with the actin cytoskeleton or even the microtubules and demonstrating the functional importance of this interaction for TRP channel function. Conversely, cation currents through TRP channels have also been found to modulate cytoskeleton rearrangements. The interplay between TRP channels and the cytoskeleton has been demonstrated to be essential for full activation of a variety of cellular functions. Furthermore, TRP channels have been reported to take part of macromolecular complexes including different signal transduction proteins. Scaffolding proteins play a relevant role in the association of TRP proteins with other signaling molecules into specific microdomains. Especially relevant are the roles of the Homer family members for the regulation of TRPC channel gating in mammals and INAD in the modulation of *Drosophila* TRP channels. This article is part of a Special Issue entitled: Reciprocal influences between cell cytoskeleton and membrane channels, receptors and transporters. Guest Editor: Jean Claude Hervé.

Contents

1. Introduction

Ion channels play an important role in a number of cellular events from volume homeostasis to the regulation of different signal transduction pathways involving fluxes of ions across the plasma membrane. Among the ion channels involved in cellular function, the cation permeable transient receptor potential (TRP) channels are specially relevant. TRP channels are non-selective cation channels initially identified in *Drosophila melanogaster* and expressed predominantly in the rhabdomeric membranes of the photoreceptor cells [1]. Since the identification of TRP proteins in vertebrates a number of members have been found, which are grouped into three major subfamilies closely related to *Drosophila* TRP, including canonical TRPs (TRPC), vanilloid TRPs (TRPV) and melastatin TRP members (TRPM), three more distantly related subfamilies, polycystin TRPs (TRPP), ankyrin TRPs (TRPA) and mucolipin TRP channels (TRPML), and a less related TRPN subfamily expressed in flies and worms [2,3]. Each subfamily contains one or more members. Structurally, TRP proteins contain six transmembrane domains, with cytoplasmic N- and C-termini, and a pore region between the transmembrane domains 5 and 6 [4]. Despite the mechanisms of activation of TRP channels is not yet completely understood, these channels are activated by a diversity of

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stimuli in many different ways. Current mechanisms include receptor occupation, exogenous and endogenous ligands or direct activation by physical stimuli. Through the use of different approaches, from overexpression to knockdown of endogenous channels and pharmacological studies, several laboratories have provided compelling evidence supporting that TRP channels are involved both in receptor-operated Ca^{2+} entry as well as in store-operated Ca^{2+} entry (SOCE) [5–11], a mechanism for Ca^{2+} influx regulated by the filling state of the intracellular Ca^{2+} stores [12]. Most TRP channels are nonselective for monovalent and divalent cations. However, there is great variability in the permeation properties of the different TRP members, with channels, such as TRPV1, that are non-selective for mono- and divalent cations [13], TRPM4 and TRPM5, which are permeable to monovalent cations and impermeable to Ca^{2+} [14,15], or TRPV5 and TRPV6, that show a high selectivity for Ca^{2+} over monovalent cations [16,17].

The location and clustering of TRP channels in specific plasma membrane domains have been reported to be essential for the regulation of their function and is mostly mediated by the association of channels with the cytoskeleton and scaffolding proteins. Alternatively, ion fluxes mediated by TRP channels have also been shown to be important for cytoskeleton rearrangements. Initial evidence supporting an interaction between TRP channels and the actin-based cytoskeleton came from studies in pulmonary endothelial cells expressing TRPC1, where Ca^{2+} entry through this channel was found to induce actin cytoskeleton remodeling required for shape change [18]. Later on, TRPC4 and TRPC5 channels were found to interact with phospholipase C via the scaffolding protein NHERF, a two PDZ domain-containing protein that associates plasma membrane proteins with the actin cytoskeleton [19]. The interaction of TRP channels with the cytoskeleton and scaffolding proteins is essential for their cellular location, and, therefore, the regulation of channel function.

2. Interplay between TRP channels and the cytoskeleton

The functional interaction of TRP channels with the cytoskeleton is bidirectional, with a role for ion fluxes through TRP channels in the rearrangement of the cytoskeletal structures and a functional role for the cytoskeleton and associated proteins supporting the appropriate location of the TRP channels, protein–protein interactions and channel gating.

2.1. Regulation of TRP channel function by the actin cytoskeleton

The role of the actin cytoskeleton on the regulation of TRP channel function has been mostly described for the TRPC family members; therefore, this section will focus specially on these channel. Nevertheless, the regulation of TRPCs as well as other TRP proteins by actin networks or actin-binding proteins is summarized in Table 1. Mammalian TRPC channels have been shown to form SOC channels, activated following the depletion of Ca^{2+} from internal stores. A number of studies have demonstrated that actin network redistribution is required for the activation of these channels in a number of cell types, including vascular endothelial cells [20], human platelets [21,22], and pancreatic acinar cells [23]. In contrast, in other cells, such as NIH 3T3 cells [24] or in smooth muscle cell lines [25] impairment of actin filament rearrangement reported no effects on the activation of SOCE. In human platelets and pancreatic acinar cells, we have found that modification of the actin cytoskeleton by stabilizing actin filaments mostly underneath the plasma membrane using jasplakinolide or calyculin A prevents the activation, but not the maintenance once initiated, of SOCE, without affecting the intracellular signaling mediated by IP_3; thus suggesting that a direct interaction between the ER and the plasma membrane might be necessary for the activation of SOCE, and cortical actin filaments might act as a physical barrier that prevents a close interaction between the ER and the plasma membrane at rest and, therefore, constitutive Ca^{2+} influx (Fig. 1). Consistent with this, platelet activation by the physiological agonist thrombin results in rapid depolymerization of actin filaments prior to the release of Ca^{2+} from the intracellular stores and the activation of Ca^{2+} entry, followed by actin polymerization. This early actin depolymerization and later polymerization is likely to be important to allow trafficking of portions of the ER toward the plasma membrane to allow the de novo coupling of TRPC1 to type II inositol 1,4,5-trisphosphate receptor (IP_3R). The actin filament rearrangement after stimulation with thrombin parallels the activation of cofilin by its dephosphorylation at Ser3. Cofilin is an actin-binding protein, regulated by the Bruton's tyrosine kinase, which disassembles actin filaments and might play an important role in the regulation of cytoskeletal remodeling upon platelet stimulation with agonists [26,27]. Moreover, impairment of actin polymerization by cytochalasin D or latrunculin A reduces SOCE activated by depletion of the ER, indicating that actin-supported intracellular trafficking is necessary of SOCE in different cell types [21,23,28]. Further studies in human platelets, where agonist-sensitive lysosomal-like acidic stores have been described [29,30], have reported that disruption of the actin network with cytochalasin D or latrunculin A enhances SOCE activated by discharge of the acidic stores; thus suggesting that the acidic stores are close enough to the plasma membrane for disruption of the membrane cytoskeleton alone to allow coupling [31]. The maneuvers to alter the actin filament network in platelets reported parallel effects in the association of TRPC1 with STIM1 [32] or the type II IP_3R [28]; thus suggesting a functional interaction between TRPC1 and the actin cytoskeleton.

Consistent with the interaction of TRP channels with the actin cytoskeleton it has been reported that TRPC4 and TRPC5 interact with the first PDZ domain of ezrin–radixin–moesin (ERM)-binding phosphoprotein-50/Na^+/H^+ exchanger regulatory factor (EBP50/NHERF), a two PDZ domain-containing protein that associates with

Table 1
Interplay between TRP channels and the cytoskeleton.

TRP	Cytoskeletal structure/protein	Function	Cell type	Reference
TRPC1	Actin cytoskeleton	Regulation of SOCE	Human platelets, pancreatic acinar cells	[21,23,26,28]
TRPC1	Microtubules	Regulation of SOCE	Human platelets	[41]
TRPC1	Actin cytoskeleton	Cytoskeletal rearrangement and shape changes	Rat pulmonary arterial endothelial cells	[18]
TRPC1, TRPC3, TRPC4	Actin cytoskeleton	Surface expression	Neutrophils	[35]
TRPC4	Protein 4.1	Activation of I_{SOC}	Endothelial cells	[33]
TRPC4, TRPC5	EBP50/NHERF	Regulation of SOCE	HEK293 cells expressing TRPC4	[19]
TRPC5	Microtubules	Neurite extension and growth cone morphology	Hippocampal neurite	[42]
TRPV1	Microtubules	Channel function and redistribution	Different cell types	[43,45]
TRPV4	Microtubules	Cell volume and motility	Different cell types	[46–48]
TRPN1	Microtubules	Signal transduction	Kinocillium	[38]
TRPP2	Microtubules	Channel function and redistribution	Renal epithelial cells, syncytiotrophoblast of human placenta	[39,40]
TRPP3	α-Actinin	Activation of channel function	Canine kidney cells	[92]
NOMPC	Microtubules	Transduction of mechanical stimuli	Cells of the sound-sensing organ of *Drosophila*	[49]

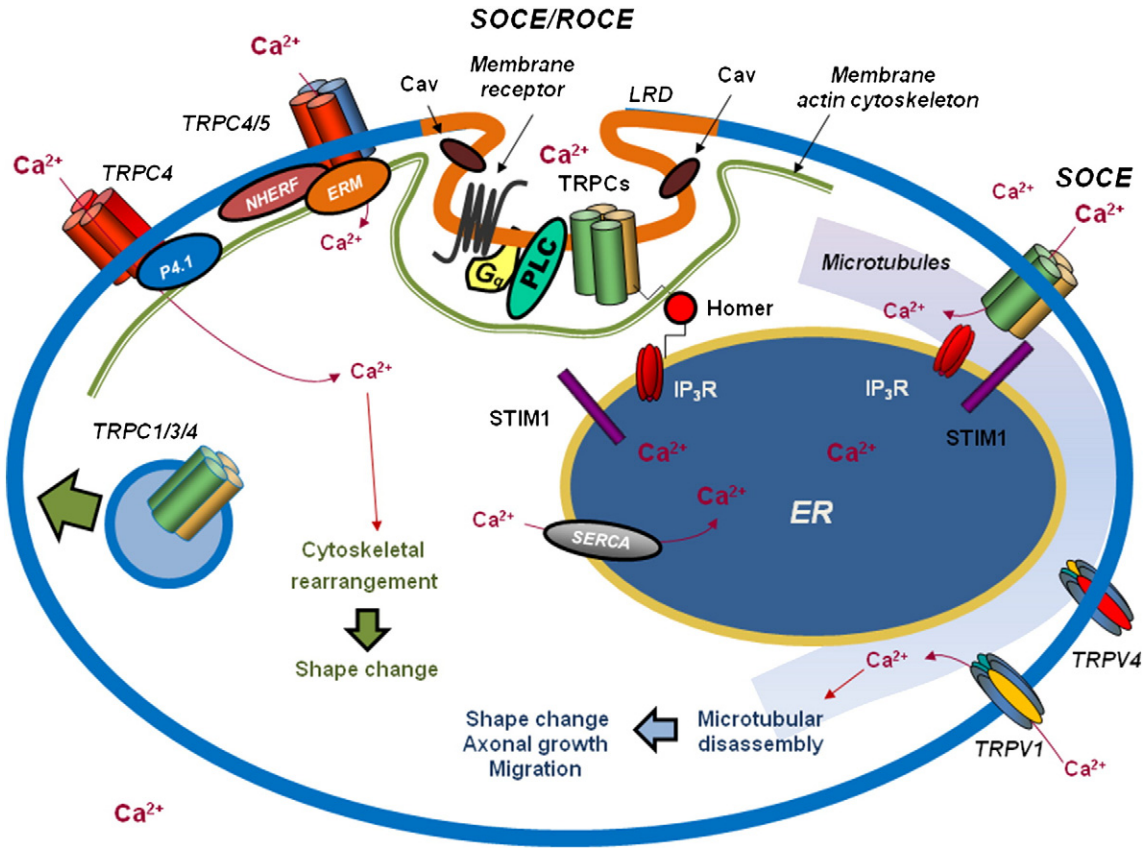

Fig. 1. Overview of the interplay between TRP channels and the cytoskeleton. The actin cytoskeleton as well as the microtubules regulates the surface expression, location and interaction of TRP channels with other signaling proteins, which allows the activation and regulation of Ca^{2+} influx activated by receptor occupation (ROCE) and/or Ca^{2+} store depletion (SOCE). Ca^{2+} entry through TRP channels results in cytoskeletal remodeling, which is required for a number of cellular processes. Cav: caveolin; ERM: ezrin/radixin/moesin; Gq: heterotrimeric G-protein; IP_3R: inositol 1,4,5-trisphosphate receptor; LRD: lipid raft domains; P4.1: protein 4.1; PLC: phospholipase C; ROCE: receptor-operated Ca^{2+} entry; SERCA: sarco/endoplasmic reticulum Ca^{2+} ATPase; SOCE: store-operated Ca^{2+} entry; STIM1: stromal interaction molecule-1; TRP: transient receptor potential channel.

the actin cytoskeleton via interactions with members of ezrin/radixin/moesin family, which may be an important mechanism for distribution and regulation of SOC channels [19] (Fig. 1). In endothelial cells, TRPC4 associates with the membrane cytoskeleton through a dynamic interaction with protein 4.1, which binds to the actin-based cytoskeleton (mediated through spectrin) a process that is necessary for the activation of I_{SOC} in these cells [33]. The C-terminal PDZ-binding motif of TRPC4 have been shown to be essential in the regulation of these channel by PIP_2, a mechanism that requires the involvement of the actin cytoskeleton and is prevented by treatment with cytochalasin D [34], which further supports a role for the actin cytoskeleton in the regulation of TRP channel function.

The involvement of the actin cytoskeleton in the surface expression of TRP channels is further supported by studies in polymorphonuclear neutrophils, where TRPC1, TRPC3 and TRPC4 expressed in the plasma membrane are internalized after cytoskeletal reorganization by calyculin A, which attenuates SOCE. The specific effect of calyculin A on actin filament reorganization was confirmed by using cytochalasin D, which disrupts the actin filament network and rescued calyculin A-induced inhibition of SOCE [35]. These results contrast with studies reporting that translocation of *Drosophila* TRPL out of the rhabdomere does not require the involvement of the actin cytoskeleton and is more likely mediated by simple diffusion through the apical membrane [36]. Altogether, these findings indicate that interaction of TRP proteins with the actin cytoskeleton depends on the cell type and the TRP protein involved.

Recent studies have reported that association of TRP channels with the cytoskeleton might require posttranslational modifications. Using the TRPV4 mutants S824D, a phosphomimicking TRPV4 mutant, and S824A, a non-phosphorylatable TRPV4 mutant, Shin et al. demonstrated that phosphorylation on the Ser^{824} of TRPV4 is essential for its interaction with the actin filaments, which is important for Ca^{2+} entry and the expansion of the surface area in transfected HEK-293 cells [37].

2.2. Regulation of TRP channel function by the microtubules

TRP channels also associate to the tubulin microtubules. Shin et al. reported location of TRPN1 at the tips and bases of the microtubule-based cilia in epidermal cells of developing *Xenopus* embryos; thus suggesting that this channel plays a functional role in signal transduction [38]. Microtubules have been reported to play an important regulatory role in the function of certain TRP channels. This is the case of TRPP2, whose function and redistribution are impaired by treatment of colchicine, a microtubular disruptor, and enhanced by the stabilizer paclitaxel both in renal epithelial cells and syncytiotrophoblast of human placenta [39,40].

The role of the microtubules supporting TRP channel function was also demonstrated in human platelets, where colchicine reduces thrombin-evoked interaction of TRPC1 with the type II IP_3R, as well as SOCE, whereas paclitaxel induced opposite effects [41]. In these cells, the role of the microtubules depends on the stimulus, which might be attributed to the different sensitivity of the two intracellular Ca^{2+} stores described, dense tubular system and acidic stores, to distinct physiological agonists [30]. Our results indicate that the microtubules play a dual role in SOCE in human platelets, both acting as a physical barrier that prevents constitutive communication between the ER and the plasma membrane channels, and also supporting the

trafficking of the acidic Ca^{2+} stores to facilitate the coupling between type II IP_3R and hTRPC1 [41] (Fig. 1).

TRPC5 channel has also been shown to interact with the growth cone-enriched protein stathmin 2, which has been associated with the regulation of neurite extension and growth cone morphology, since dominant-negative TRPC5 expression resulted in significantly longer neurites and filopodia [42].

In addition to TRPC proteins, TRPV channels are regulated by microtubules. The interaction of TRPV1 with the microtubules was first identified in the neuronal tissue through a proteomic screen for proteins associated with the C-terminal sequence of TRPV1 [43]. TRPV1 was found to bind tubulin dimers, as well as polymerized microtubules [43]. The tubulin-binding region within the C-terminus of TRPV1 was mapped to two regions between amino acids 710–730 and 770–797 [44]. TRPV1 preferably interacts with β-tubulin and to a lesser extend with α-tubulin [44]. The association of microtubules with TRPV1 is enhanced by increasing Ca^{2+} concentrations [43] and, at resting state, the association with TRPV1 stabilizes the microtubules [43]. A recent analysis has also revealed a tubulin binding sequence-1 (TBS-1) near the TRP-box of TRPV1 that has evolutionary significance, since this interaction may be required not only to the surface expression and location of TRPV1 but for the adequate channel function and regulation [45]. Other TRPV proteins, such as TRPV4, have also been associated with the microtubules. Although the functional relevance of the interaction of TRPV4 with the microtubule cytoskeleton remains mostly unknown, TRPV4 has been shown to be involved in the development of taxol-induced mechanical hyperalgesia (the microtubule stabilizer taxol reduces TRPV4-mediated currents) [46,47]. In addition, the interaction of TRPV4 with the microtubule cytoskeleton is associated with the regulation of cell volume [46,47] and cell motility [48].

The microtubular network has also been found to be important for the activation and function of the protein NOMPC, a member of the TRPN ion channel family expressed in the tubular body of campaniform receptors in the halteres and the distal regions of the cilia of chordotonal neurons in Johnston's organ, the sound-sensing organ of *Drosophila*. In these cells, NOMPC associates with the microtubules, which suggests a transmission route of the mechanical stimulus to the cell [49].

2.3. Regulation of cytoskeletal remodeling by TRP channels

The cytoskeleton might act both as a modulator and a modulated downstream effector of TRP channel function. The latter has been reported in different cellular models. In rat pulmonary arterial endothelial cells, actin rearrangement is regulated by the elevation in cytosolic Ca^{2+} concentration; however, cytoskeletal rearrangement has been reported to be differentially regulated by Ca^{2+} entering the cells and Ca^{2+} released from intracellular pools, with Ca^{2+} influx, probably mediated by TRPC1, being necessary for the remodeling of the actin cytoskeleton that supports cell shape changes [18].

Moreover, in contrast to the stabilization of microtubules at resting state upon association with TRPV1, activation of TRPV1 results in rapid disassembly of microtubules in all the cell types investigated [50–52]. TRPV1 activation in F11 cells leads to disorganization of peripheral microtubules, whereas the microtubular networks close to the microtubule-organizing center and the perinuclear region remain intact [50–52]. Disassembly of microtubules by TRPV1 activation has been reported to play a functional role on axonal growth, morphology and migration [50] (Fig. 1). By contrast, TRPV1 activation has no depolymerizing effects on the actin cytoskeleton and even an increase in the actin filament content has been described upon TRPV1 activation [53].

3. Modulation of TRP channel function by scaffolding proteins

Scaffolding proteins have been shown to play an important role in TRP channel function. Segregation of TRP channels induced by interactions with adaptor proteins determines their localization and modulation in different functional microdomains. Among the scaffolding proteins involved in the regulation of TRP channels, Homer proteins deserve a special distinction. Homers are a family of adaptor proteins including Homer1, Homer2 and Homer3, with numerous isoforms in mammals, and identified in the brain [54]. Orthologs of the Homer proteins have been identified in other animal species including *Drosophila* [55], *Xenopus* [56] or zebrafish [57], but not in eukaryotes outside the animals [58]. The short murine Homer1a isoform (186 amino acids in length) was the first to be isolated. The Homer proteins are predominantly located at the postsynaptic density in mammalian neurons acting as adaptor proteins for many postsynaptic density proteins. Homer1a has been shown to be upregulated in response to synaptic activity activated by seizure and during long-term potentiation.

The Homer adaptor proteins contain an Enabled/vasodilator-stimulated phosphoprotein (Ena/VASP) Homology 1 (EVH1) domain. Homer1a presents a short C-terminus, whereas Homer 1b and 1c are longer isoforms containing, in addition to the EVH domain, a coiled-coil domain, which allows the formation of homo- and heterocomplexes of Homer proteins, and two leucine zippers (Fig. 2). Finally, Homer1 presents different proline-rich peptide binding sites (aa 24, 70, 74 and 89) [59–62]. Homer1 consists in a class II EVH1 (Ena (Enabled)/VASP (vasodilator-stimulated phosphoprotein) homology 1) domain, which binds to a number of ligands, including PPxxF or LPSSP amino acid motifs, present in different Ca^{2+}-handling proteins such as $PLC_β$, IP_3Rs, ryanodine receptors, TRPC channels, the voltage channel $Ca_v1.2$ and STIM1 [60,62–65].

Homer1 has been proposed as essential to regulate TRPC channel function. Studies performed in HEK293 cells expressing TRPC1 and Homer1 reported that the latter was found to maintain TRPC1 in the closed configuration, which associated with IP_3Rs and supported by Homer proteins keep the channel inactive. The studies performed by Yuan and coworkers demonstrate that the filling state of the ER dynamically controls TRPC1–Homer and TRPC1–IP_3R associations. Thus, discharge of the intracellular Ca^{2+} stores results in dissociation of TRPC1–Homer complex, which coincides with activation of TRPC1 and SOCE, while store refilling leads to assembly of the TRPC1–Homer–IP_3R complex and coincides with the inactivation of SOCE [65]. Dissociation of TRPC1 from Homer proteins might allow the interaction of TRPC1 with STIM1 to activate SOCE [66]. Direct gating of TRPC channels by STIM1 has been demonstrated by mutational and functional analysis, which showed that the two terminal STIM1 lysines K684 and K685 communicate electrostatically with the conserved DD/E residues located at the C-terminus of the TRPC channels [67]. The regulatory role of Homer1 is also supported by the enhanced spontaneous Ca^{2+} influx in cells from Homer1$^{-/-}$ knockout mice [65]. In human platelets, we have recently reported a regulatory role of Homer1 on TRPC1-type II IP_3R and STIM1–Orai1 interactions [68]. In these cells, discharge of the intracellular Ca^{2+} stores using thapsigargin or the physiological agonist, thrombin, leads to Ca^{2+}-independent association of Homer1 with TRPC1 and the type II IP_3R, as well as the association of Homer1 with STIM1 and Orai1, in this case occurring in a Ca^{2+}-dependent manner. Interference with Homer function by introduction of the synthetic PPKKFR peptide into cells, which emulates the PPxxF motif, attenuates STIM1–Orai1 and TRPC1-type II IP_3R association, as compared with the respective control performed with the inactive PPKKRR peptide. Impairment of Homer function attenuates thrombin-evoked Ca^{2+} entry and the maintenance of SOCE, consistent with our previous studies reporting a role of the TRPC1-type II IP_3R interaction in the maintenance of SOCE in these cells [69], as well as platelet aggregation. The differences in the results observed in human platelets, where store depletion results in association of Homer1 with TRPC1 and IP_3R, and the previous studies in transfected HEK293 cells and murine cells might be attributed to the idiosyncrasy of the cells investigated.

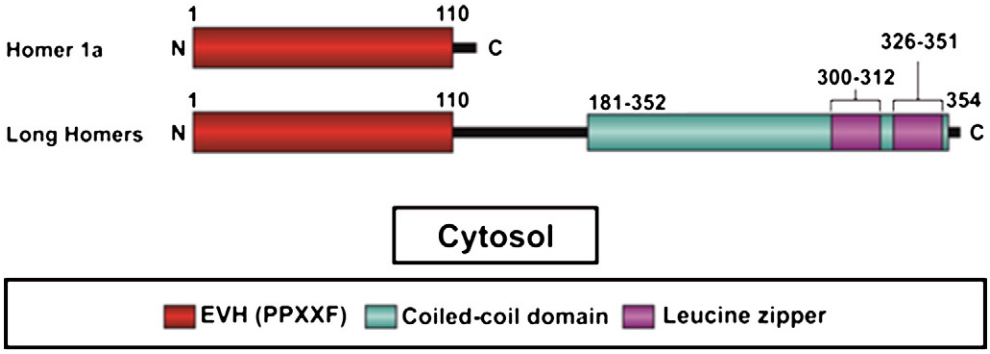

Fig. 2. Structure of Homer proteins.

Nevertheless, both studies report a relevant role of Homer proteins in TRPC channel function.

TRP channel function is also regulated by their location in plasma membrane domains, called caveolae. Caveolae are small invaginations of the plasma membrane formed through a coalescence of lipid raft domains and maintained due to the presence of the protein caveolin. There are three homologous genes of caveolin expressed in mammalian cells: Cav1, Cav2 and Cav3. Caveolin-1 is a cholesterol-binding protein, enriched in lipid raft domains, that plays an important role in the recruitment/association of specific proteins into lipid rafts [70], thus participating in the coordination of cellular signaling events [71]. TRPC1 has been found to be associated with caveolae in the plasma membrane of human salivary gland cells, where it interacts with different signaling proteins, including caveolin-1, type 3 IP_3R and $G_{\alpha q/11}$ [71]. The integrity of the lipid raft domains plays a critical role in the activation of SOCE [71]; thus suggesting that recruitment of signaling proteins, including TRPC1, in caveolar lipid raft domains is essential for the regulation of SOCE. TRPC1 has also been found to co-immunoprecipitate with caveolin-1 in spermatogenic cells [72], endothelial cells [73], and, despite caveolin protein expression has not been described, in human platelets, where the association of this channel with lipid raft domains has been demonstrated to be essential for the activation of Ca^{2+} influx [74–76]. In addition to TRPC1, other TRPC proteins associate with caveolar lipid raft domains, including TRPC4, whose interaction with the IP_3R upon agonist stimulation is facilitated by the interaction with caveolin-1 [73], TRPC3, TRPC6 and TRPC7 [71,77,78]. Caveolae are a subset of lipid rafts. This cholesterol and sphingolipid-enriched membrane microdomains have been reported to play an essential role in the formation of signaling complexes associated with the regulation of receptor-dependent mechanisms, including SOCE. A number of studies have provided evidence for the formation of a macromolecular store-dependent complex required for the activation and regulation of SOCE and including the proteins STIM1, TRPC1, Orai1 and SERCA among others [79].

In addition to Homer proteins and the caveolin-scaffolding lipid raft domains, other adaptor proteins have been found to associate with TRP channels and to regulate their function. *Drosophila* TRP channels links the adaptor protein INAD (inactivation no afterpotential D), a PDZ domain-containing protein which, in turn, associates TRP channels with other regulatory proteins, including rhodopsin, phospholipase C, protein kinase C, calmodulin and the immunophilin FKBP59 [80,81]. PDZ domains support the association of anchor transmembrane proteins to the cytoskeleton and maintain together signaling complexes. Impairment of the association of TRP channels with INAD, as found in the InaDP215 mutants, results in a defect in the termination of the light response by promoting efficient phosphorylation at Ser982 of TRP for fast deactivation of the visual signaling [82,83]. By contrast, INAD has been reported as not essential for TRP channel function in *Drosophila* Malpighian (renal) tubules [84].

In mammalian cells, TRP proteins are associated to a number of scaffolding proteins. The last three C-terminal amino acids (TRL) of TRPC4 comprise a PDZ-interacting domain that is able to bind to the scaffold protein EBP50/NHERF. Using immunofluorescence microscopy and biotinylation experiments, it has been reported that a TRPC4 mutant lacking the TRL motif accumulated into cell whereas the wild-type channel was evenly distributed on the plasma membrane in HEK-293 cells. Furthermore, in cells expressing an EBP50 mutant lacking the ERM-binding site, TRPC4 was no expressed in the plasma membrane but co-localized intracellularly with the truncated EBP50. Altogether, these findings provide evidence for a role of the PDZ-interacting domain of TRPC4 and the scaffold protein EBP50 in the localization of TRPC4 in the plasma membrane [85]. In addition, colocalization of TRPC4 with the scaffolding protein zonula occludens 1 (ZO-1) has been demonstrated by immunoprecipitation with antibodies in astrocytes, thus suggesting that TRPC4 takes part of a signaling complex that forms at junctional sites between astrocytes [86]. Furthermore, it has been shown that the sensitivity of the heat-activated ion channel TRPV1 is modulated by the protein kinases PKA and PKC and by the phosphatase calcineurin, an event that depends on the formation of a signaling complex between these enzymes,TRPV1 and the scaffolding protein AKAP79/150 [87].

Other adaptor proteins involved in the regulation and function of TRP channels include RACK-1 (receptor for activated C kinase 1), a scaffolding protein that inhibits channel function of the TRP channel TRPP3 [88] and modulates the association of TRPC3 with a number of proteins including the type I IP_3R, STIM1 and Orai1 [89,90]. Filamins have recently been reported to be important regulators of TRPP2 channel function through a dynamic interaction with the actin cytoskeleton [91] and caveolins have been shown to associate TRPC1 with lipid raft domains [71].

4. Concluding remarks

TRP channels play an important functional role in intracellular Ca^{2+} homeostasis in response to occupation of a number of receptors, intracellular Ca^{2+} store depletion or different stimuli such as temperature, touch, pain or osmolarity. The correct location of TRP channels into macromolecular complexes in specific cellular microdomains is essential for channel function. TRP channels interact with the actin filaments and microtubules, as well as with cytoskeleton-binding proteins, which supports the surface expression of these channels and the insertion into specialized microdomains. Furthermore, these channels also associate with scaffolding and adaptor proteins, which play a relevant role in the association of TRP channels with other signaling molecules. The specific interaction of TRP channels with scaffold and adaptor proteins and with the cytoskeleton might be responsible for the different behavior sometimes reported in the literature for these channels in endogenously expressed and transfected cells.

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