Right time–right location–right move
TRPs find motors for common functions

Rakesh Majhi,1,† Puspendu Sardar,1,† Luna Goswami2 and Chandan Goswami1,*

1National Institute of Science Education and Research; Institute of Physics Campus; School of Biotechnology; KIIT University; Bhubaneswar, Orissa India
2School of Biotechnology; KIIT University; Bhubaneswar, Orissa India

*These authors contributed equally to this work.

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TRP channels are localized at specialized sub-cellular compartments like filopodial tips, ciliary structures, growth cones and spines that have importance in the context of several sensory functions. Several motor proteins largely regulate these localizations. Recent studies indicate that both physical and genetic interactions exist between TRP channels with actin and microtubule-based motor proteins. These two groups of proteins share specialized and fine regulation underlying physiological functions. Indeed, mutations causing loss of these interactions and regulations result in development of pathophysiological disorders and syndromes. In this review we analyze the recent progress made in cell-biological, biochemical, electrophysiological and genetic studies and summarize the multi-dimensional crosstalk between TRP channels with different motor proteins.

Introduction

So far TRP channel research in the context of pathophysiological disorders was exclusively focused on the ionic conductivity mediated by these channels. It was not until recently that regulation of TRP channels localization and non-ionic functions of TRP channels in the context of different pathophysiological disorders has emerged. A handful studies have characterized physical and other functional interactions of TRP channels with different cytoskeletal components. For example, several TRP channels show physical interaction with tubulin, actin and other cytoskeletal associated components like MAPs, actinin, different motor proteins, other scaffold proteins and regulatory proteins.1–3 Interestingly, many of these interactions are regulated by phosphorylation or other modifications and are Ca2+-independent in nature. Therefore, these interactions have important roles in executing the non-ionic functions and regulations of TRP channels per se. In this context, motor proteins not only play an important role in recruiting the TRP channels in proper subcellular locations, but they also regulate recycling as well as other functions of TRP channels. Thus motor proteins play an important role in maintaining the proper function of TRP channels.

Apart from coexpression and colocalization, the physical and functional crosstalk between TRPs and motors is evident from several genetic studies, too. In many cases, the development and the function of these specialized cellular structures like cilia, filopodia, spine etc., are regulated by both TRP channels and cytoskeletal proteins. Notably, mutations in either TRP channels or specific cytoskeletal proteins often lead to similar, if not same cellular phenotype, as well as same pathophysiological disorders like deafness, blindness, and other syndromes. Taken together, involvement of these two groups of proteins in common functions and occurrence in the same cell (even in the same sub-cellular locations) are highly indicative of physical, functional and genetic interactions.4 Based on the available data, in this review we critically analyze the latest understanding of the multi-dimensional relationship between TRP channels and motor proteins. We also summarize how different motor proteins and TRP channels regulate one another. We also point out how these two groups of proteins are involved in important cellular and physiological processes as well as in common functions.

Clue from Expression and Co-Localization

The importance of different cytoskeleton and associated motor proteins in the context of function and regulation of TRP channels came from the common observation that these channels and the specific motor proteins are co-expressed in some specialized cells. In addition, TRPs and the motor proteins are located at distinct subcellular structures that are characterized not only by the presence of these specialized cytoskeletal proteins, but also by the intricate organization and specific localization of the TRP channels there. This strongly suggests that TRP channels either interact with some of the cytoskeletal proteins and/or are involved with the development as well as function of these subcellular structures. Indeed, evidences suggest so. For example, both PC1 and PC2 (alternatively known as TRPP channels) are present in the primary cilium of kidney cells.5 PC2 channel is also localized at the primary cilia of renal epithelial cells.6 In addition, PC2 channel co-localizes with polyglutamylated tubulin at the basal bodies/cilia of the ciliated epithelial cells from mouse trachea.7 PC2 also forms a complex with pericentrin (a marker for centrosome and basal body), and this interaction is required for primary cilia assembly.7 Involvement of PC2 in the

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ciliary function has been demonstrated in agreement with these reports. The localization of PC channels at the tip (plus end of microtubule), as well as at the basal body (minus end of microtubules) of the cilium in general, suggest that PC channels recycle within the cilium; and this localization is involved in the proper development and function of the cilium in addition to recycling.

Like PC channels, Xenopus TRPN1 localizes at the tip of microtubule-based cilia in epithelial cells (kinocilial bulb) and at the tip of the inner-ear hair cells. There TRPN co-localizes with cytoskeletal components like actin, tubulin and Cdh23. In Drosophila melanogaster, NOMPC (a member of the TRP channel family) localizes to the tubular body and distal cilium of Campaniform and Chordotonal receptor cells and is involved in ciliary functions. TRPN (=NOMPC) localizes at the distal end of mechanosensory cilia and localizes with EYS (an extracellular protein that marks the proximal end of the sensory cilium) in Drosophila. TRPC6 localize in podocytes where they interact with podocin and nephrin, components which belong to the actin cytoskeleton. These examples strongly suggest that the localization of TRP channels in polarized and differentiated cells are specific in nature and that TRP channels share a special relation with the cytoskeletal organization.

Recently we have demonstrated that when expressed, TRPV1 is localized at the tip of filopodia in both neuronal and non-neuronal cells. Similarly, TRPV4 is also located at the filopodial and lamellipodial structures; and in a same manner, endogenous TRPV4 is also present in the cholangiocyte cilium. Expression of TRPV1 induces filopodial structures which reveal the presence of a characteristic bulbous head. Interestingly, these heads often contain negligible amounts of F-actin but accumulate TRPV1 there. This phenotype and localization of TRPV1 resemble well with the dominant-negative effect of non-conventional myosin motors. This is mainly due to the fact that overexpression of myosin II, III, V, X and XV is known to induce filopodial structure of same morphology, and these myosin motors also localize at the bulbous head regions. Such similarities suggest that overexpression of TRPV1 may alter the function of these myosin motors. Indeed, we have demonstrated changes in the expression pattern as well as distribution of non-conventional myosin IIa and IIa after the ectopic expression of TRPV1. Overexpression of TRPV1 in F11 cells results in more expression as well as reorganization of endogenous myosin IIa and IIa. In agreement with this observation another study has also confirmed that overexpression of TRPC6 in transgenic mice resulted in an increased expression of beta-myosin heavy chain in cardiac tissues. However, the exact mechanisms and reasons behind these altered expression and distribution of non-conventional myosin motors are not yet known.

So far several TRP channels have been detected in the spines, which is consistent with the localization of TRP channels at the filopodial tips. This is due to the fact that spines and filopodial structures share structural, morphological and functional similarities. Endogenous localization of several TRPV and TRPC members have been detected at the spines, which are involved in the neuronal network formation. Therefore, the crosstalk between TRP channels and non-conventional myosin motors are relevant in terms of spine development and maintenance of spine and growth cone organization (discussed later).

**Genetic, Functional and Physical Interaction and Effect of Mutations**

Conclusive examples have yet to come from genetic studies that establish multi-dimensional crosstalk of TRP channels with different motor proteins. Most of these examples highlight the common involvement of TRP channels and motor proteins in different sensory functions that are mediated by cilia, filopodia and/or other polarized cellular structures. For example, study of Polycystic Kidney Disease (PKD) mutants reveals that many ciliary proteins as well as PCI and/or PC2 are involved with this disease. Mutations in PCI and PC2 results in defective localization of these channels, impaired cilia formation, and/or loss of flow-induced Ca2+-signaling, which are relevant in the context of PKD. These results are also consistent with the fact that PC channels are regulated by microtubule-based motor proteins like KIF3a and KIF3b. In a similar context, both KIF1b and TRPV4 are involved in some common functions like mechanosensation suggesting a strong genetic link between them. This is also supported by the fact that mutations in either kinesin (Kif1b) or TRPV4 results in same pathophysiology and development of Charcot-Marie-Tooth disease type 2 (CMT2).

Like kinesins, myosin motors are also involved in the regulation of TRP channels. Mutations in TRP channels as well as in different non-conventional myosin motors develop similar pathophysiological disorders and other syndromes like deafness, blindness, and other sensory defects. For example, both development and proper function of the stereocilia of hair cells are important for hearing. In normal conditions, the ciliary tips of hair cells contain several endogenous TRP channels as well as several non-conventional myosin motor proteins, indicating that the function of these cells is largely dependent on these two group of proteins at the ciliary tips. Several reports suggest that in case of deafness, non-conventional myosin motors (myosin I, IIA, IIIA, VI, VIIA and XV) are important for either development of the stereocilia of hair cells in the inner ear or proper localization of TRP channels at the tip of these stereocilia. In a reciprocal manner, so far, TRPN1, TRPV4, TRPML3 and TRPA1 have been detected in the vertebrate inner ear. Consistent with these reports, either mutation, deletion or abnormal expression and function of these TRP channels (namely TRPA1, NompC, TRPML1, TRPML2, TRPML3, TRPV4, TRPV5 and TRPV6) result in the development of deafness.

Comparable to auditory defects, development, polarization of retinal cells and proper trafficking of pigments in the retinal cells are involved in proper light-sensing mechanisms. Both TRP channels and non-conventional myosins are involved in blindness. Retrospectively, the TRP channel was first discovered by Minke et al. in Drosophila melanogaster as the trp-mutant reveals defective light-sensing mechanisms. Indeed, so far several TRP channels have been reported to express in retinal cells. Some of these TRP channels are involved in photo-response and are essential for light sensation, as mutations in these TRP...
channels cause different forms of blindness. \(^5\)
For example, mutation in TRPM1 is responsible for blindness because it is involved in retinal ON bipolar function. \(^5\) In agreement with the involvement in common function, mutations in myosin motors are also involved in blindness. For example, mutation in myosin VIIa is involved in the development of “Usher-syndrome type 1B”. \(^4\) In Drosophila, \(Ca^{2+}\)-activated myosin V is involved with the closure of the pupil, and thus, is involved with light sensation. \(^6\) It has also been reported recently that translocation of eGFP-tagged TRP-like channels to the rhabdomeral membrane in Drosophila photoreceptors is myosin III dependent. \(^7\) These reports indicate genetic as well as functional interactions between TRP channels and myosin motors and suggest possible physical interactions, too. In fact, a recent proteomic screen has identified myosin as an interacting partner for TRPC5 and TRPC6. \(^8\) Another recent study showed that myosin IIa is directly phosphorylated by TRPM7, a cation channel fused to an alphakinase. \(^9\) TRPM7 phosphorylates positively charged coiled-coil domain of myosin II, and this phosphorylation in turn regulates cell contractility and adhesion. \(^1\) In the same notion, a recent proteomic screen has identified Myosin 10 as an interacting protein of TRP5. \(^2\) All these results suggest that TRP channels and some of the specific cytoskeletal proteins such as non-conventional myosin motors and other kinesins are involved in the same functions. However, further studies are needed to understand these interactions and their significance in detail.

### TRP and Motors in the Transition of Cell Morphology

A significant understanding of the common function between TRP channels and motor proteins can be derived from the observation that expression as well as activation of TRP channels often result in changes in the cellular structure, morphology and causes major transitions. For example, ectopic expression of TRPV1 results in induction of excessive filopodial structures and elongation of neurites. \(^2\) By contrast, activation of TRPV1 by RTX results in retraction of growth cone and varicosity formation. \(^4\) This cellular retraction and varicosity formation is largely due to the disassembly of microtubules caused by activation of TRPV1. \(^4\) Due to the sudden loss of microtubules, the retrograde force mediated by the actin cytoskeleton, (mainly produced by the myosin motors) overrides the anterograde force produced by the microtubule cytoskeleton. The growth cone retracts and neurites develop multiple varicosities or “beads-in-a-string” morphology as a result of this unbalanced force (Fig. 1). \(^2\) Activation of TRPV1 by RTX results in rapid elongation of filopodial structures as well. \(^2\) Similarly, activation of TRPV1 by NADA, an endogenous component, also results in rapid elongation of filopodial structures and dendritic spines. \(^2\) As filopodial and/or dendritic spine elongation need supplies of extra membrane, these results strongly suggest that activation of TRPV1 leads to vesicle fusion at the filopodia and/or spine. We actually confirmed vesicle fusion at the base of the filopodial structures after activation of TRPV1. \(^2\) We also confirmed active movement and trafficking of vesicles carrying TRPV1 within the growth cone and filopodial structures. \(^2\) Though the identities of such motors are still unknown, these studies strongly suggest the involvement of different motor proteins that are required for several specific jobs relevant for growth cone turning or elongation (Fig. 2). This notion is supported by several facts. First, the movement of cytoplasmic transport packets (CTPs) towards the C- and T-zone of the growth cone is mainly based on microtubule cytoskeleton. In addition, movement of vesicles (and
processes. However, it seems that TRP channels also regulate such processes in a Ca\(^{2+}\)-independent manner by regulating unconventional motor proteins and Ca\(^{2+}\)-independent kinases, an area which is still not well understood. In normal scenario, Ca\(^{2+}\)-dependent processes often overshadow non-ionic functions of TRP channels. However, there are several examples that support regulatory roles of TRP channels, which are primarily independent of Ca\(^{2+}\)-influx activity. For example, TRPV1-ΔNt (truncated channel which cannot conduct Ca\(^{2+}\)-influx) induces massive filopodial structures from all over the cells (Fig. 3).\(^{12}\) In addition, estrogen-induced cytoskeletal reorganizations are TRPV1-dependent, but they are independent of TRPV1 channel activity.\(^{68}\) Often TRPV1-dependent cytoskeletal reorganization cannot be blocked by the presence of extracellular EGTA and \(5'I\)-RTX.\(^{12,64,68}\) These facts suggest that TRPV1-mediated reorganization of cytoskeleton is at least partially Ca\(^{2+}\)-independent. It seems that different Ca\(^{2+}\)-dependent and -independent kinases are involved in such processes. Taken together, recent results indicate that TRPV1 acts as a scaffold at the plasma membrane, and this scaffolding act is important for Ca\(^{2+}\)-independent functions and critical for certain signaling events. However, further studies are needed to understand the exact mechanisms behind these transitions and dissect the role of different types of myosin motors in that context.

Regulation of TRP Channels Conductivity by Cytoskeletal Proteins

A number of previous studies have demonstrated that the ionic conductivity via TRP channels is altered if the integrity and/or...
dynamics of different cytoskeleton are altered by means of pharmacological agents. For example, Ca\(^{2+}\)-influx via TRPV4 is altered if actin or microtubule cytoskeletons is/are altered.\(^{13,60}\) These changes in most cases reflect the alteration in the number of TRP channels present in the membrane. This is mainly due to the fact that alteration of cytoskeleton simply affects the localization, trafficking and recycling of TRP channels. Thus, these results do not indicate if there is any change in the properties at the level of single channel complex.

However, in recent time very few studies have addressed this problem and attempted to establish a direct regulatory role of the cytoskeleton on the channel activity. In this aspect, the best characterization has been done on TRPP channels.\(^{32,70}\) PC2 channels isolated from vesicles were reconstituted on lipid bilayers, and subsequently single-channel recordings were performed. This system arguably eliminates all other regulatory and cellular factors except the channel-associated complex. Interestingly, actin, the actin-related components such as α-actinin and gelsolin, tubulin including acetylated α-tubulin, and the kinesin motor proteins (KIF3A and KIF3B) are present in these membranes, suggesting direct interaction of these components with PC2 channels.\(^{32,70}\) It has been demonstrated that cytoskeletal components indeed regulate the properties of PC channels. Disruption of actin filaments by addition of actin-severing protein like gelsolin or by addition of cytochalasin-D activates PC2 channel. This actin-mediated activation of PC2 can be inhibited by inducing actin polymerization, especially by addition of soluble monomeric G-actin with ATP. This indicates that actin filaments—not soluble actin—are an endogenous negative regulator of PC2 channels. Similarly, microtubules also regulate PC2 channel function but in an opposing manner. Depolymerization of microtubules with colchicine rapidly inhibits the basal level of PC2 channel activity. In contrast polymerization and/or stabilization of microtubules by addition of GTP and taxol\(^*\) to soluble tubulin stimulate(s) PC2 channel activity.\(^{70}\) Involvement of the microtubule cytoskeleton in the regulation of PC2 channel has also been described in vivo in primary cilia of renal epithelial cells.\(^{6}\) In that system, addition of microtubule destabilizer (colchicine) abolishes channel activity rapidly, whereas the addition of microtubule stabilizers (taxol\(^*\)) increases channel activity.\(^{6}\) Similar results were obtained using reconstituted lipid bilayer system, revealing that both spontaneous activity and the opening probability of TRPP3 ion channels are increased by the addition of α-actinin, thereby demonstrating that the channel properties can be modulated by cytoskeletal components.\(^{71}\)

**Figure 3.** TRPV channels regulate filopodia development and function. Shown are the confocal images of filopodial structures of different length, shape and structures developed from cells expressing TRPV1-GFP (A–E) as well as truncated version (F) TRPV1-ΔCt that is defective in Ca\(^{2+}\)-conductance. TRPV1-induced filopodial structures can form even in the presence of 5′I-RTX (E) indicating that development and regulation of such entities need TRPV1 but are independent (at least in part) of Ca\(^{2+}\)-influx mediated by TRPV1.

**Conclusion and Future Direction**

The multidimensional crosstalk between TRP channels and different motor proteins is just emerging. So far only a few motor proteins have been identified that can interact with these TRP channels directly. Until now the interacting regions, their binding kinetics and the precise regulations are not known. However, such information will be beneficial to understand how TRPs and...
different motor proteins join hand-in-hand for common functions. This may in turn have significant relevance in different pathophysiological disorders as TRP channels can be targeted by different physical and chemical stimuli at pharmacological doses. Such strategies may prove useful against different neurodegenerative diseases where TRPs and different motor proteins control neuronal migration, spinal development and functions. In the same context, such an understanding may also be useful for other immunological diseases where cellular migration, attachment, and morphological changes of immune cells are involved in several functions. In different cellular systems, how TRP channels actually regulate the motor proteins and induce cytoskeletal reorganization, thereby coordinating different functions, remains to be explored in future.

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