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TRP Ion Channels: From Distribution to Assembly

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Abstract

Transient receptor potential (TRP) ion channel superfamily is widely distributed from neuronal to non-neuronal tissues by serving as cellular sensors via interacting with a wide spectrum of physical and chemical stimuli. TRP ion channels are tetrameric protein complexes. Accordingly, TRP subunits can form functional both homomeric channels and heteromeric channels which either in the same subfamily or in the different subfamilies to diversify TRP channel functions. In this chapter, we will briefly introduce this fascinating ion channel superfamily. Further, we will summarize current knowledge on mammalian TRP ion channels distribution in tissues and organs as well as assembly of these ion channel subunits. Implications and related physiological roles regarding distribution and assembly will be overviewed as well.

Keywords: assembly, expression, interaction, ion channel, tetramer, TRP

1. Introduction

Mammalian TRP ion channel superfamily comprises 28 members, which belong to 6 subfamilies including TRPC (TRPC1-7), TRPV (TRPV1-6), TRPM (TRPM1-8), TRPML (TRPML1-3), TRPA (TRPA1) and TRPP (TRPP2, TRPP3 and TRPP5). Most of the TRPs are non-selective cationic ion channels, which permeate to Ca^{2+} , Mg^{2+} and Na^{+} cations, and involve in a plethora of physiological and pathological functions.

Despite as low abundant membrane proteins, TRP ion channels are widely distributed in tissues and organs in mammals. TRPs can be activated by diverse physical or chemical stimuli in nature which make these ion channels as multifunctional cellular sensors [1].

TRP ion channels are tetrameric cation channels. Structurally, each TRP subunit harbors six transmembrane segments with a pore-forming region. Both N and C termini are located intracellularly. Most of the TRPs have an ankyrin repeat domain in N terminal and a TRP box in C terminal by modulation of protein-protein interactions that allowing intra- and inter-cellular associations. The long N and C termini of TRPs also contain several additional regulatory regions, which are relatively conserved in most of the TRP channels.

2. Distribution and function of TRP channels in tissues and organs

2.1. TRPs in nervous system

2.1.1. Distribution patterns

TRP ion channels are widely distributed in nervous system harboring members among subfamilies of TRPC, TRPV, TRPM, TRPA and TRPML. These TRPs can be detected both within central and peripheral nervous system. Briefly, TRPCs are extensively distributed in various parts of mammalian brain and DRG neurons. Specifically, TRPC1 is characterized distributed in mammalian brain, including human fetal and adult brain, rat brain as well as rat embryonic brain [2].

For TRPVs, all members of this subfamily are expressed in central nervous system. TRPV1 has been detected in mammalian brain, especially one study revealed that TRPV1 exhibited highly restricted distribution in central neuronal system in rat, monkey and human by using in situ hybridization as well as electrophysiological recordings [3]. Recent studies reported that TRPV5 was detected in olfactory bulb, cortex, hippocampus, hypothalamus, midbrain, brainstem and cerebellum of the rat [4]. In addition, TRPV6 was found in lamina terminalis, olfactory bulb, amygdala, hippocampus, brainstem and cerebellum of the mouse [5].

Among TRPM subfamily, TRPM1 and TRPM2 are widely expressed in mammalian brain. Moreover, other members of this TRPM subfamily, including TRPM3, TRPM4, TRPM5, TRPM7 and TRPM8, were all identified expressed in rat, mouse and human brain [6].

Further, TRPA1 was extensively found in mammalian sensory ganglia, trigeminal sensory afferents and spinal dorsal horn, even in astrocytes [6, 7]. TRPV4 and TRPA1 were detected in pancreatic nerve fibers and in dorsal root ganglia neurons innervating the pancreas, which may contribute to inflammatory pain in mice [8].

The three members of TRPML are all expressed in mouse brain [9].

2.1.2. Specific molecular sensors

Based on the distribution pattern of TRP ion channels in nervous system, their multi-functions as cellular sensors are consistent with the complexity of nervous network. Specifically, TRPV1, TRPV2, TRPV3, TRPV4 and TRPM2, TRPM3, TRPM4, TRPM5 are characterized as

heat and warm sensors of body so far, while TRPC5, TRPM8 and TRPA1 are responsible for cold or cool sensing [10]. Meanwhile, continuous studies revealed that TRPM1, TRPM4, TRPC1, TRPC3, TRPC5 and TRPC6 may involve in auditory mechanosensation [11–13]. TRP ion channels serving as cellular sensors are also involved in taste via TRPM5, pain by TRPV1, TRPV2 and TRPA1 [14]. In addition, most TRP ion channels may involve in olfactory transduction by widely distributed in olfactory bulb [15].

2.2. TRPs in skeletal system and implications

2.2.1. Distribution patterns

In general, skeletal system consists of bone, joint and skeletal muscles. Recent studies have been elucidated that several members of TRPCs, TRPVs and TRPMs are distributed in these organs and tissues. Specifically, TRPC1 and TRPC4 have been detected in bone and skeletal muscles [16, 17].

Further, TRPV2 was detected in osteoclasts in bone [18]. TRPV4 has been found in mandibular condylar chondrocytes, osteoclasts and osteoblasts of the rat [19, 20]. TRPV5 appeared in the ruffled border membrane of the mouse osteoclasts, and TRPV6 was observed widely expressed in bone cells but was not crucial for bone mineralization in mice [21].

Moreover, human TRPM7 has been found in bone, and recent study revealed that TRPM7 regulated Mg^{2+} ions to promote the osteoinduction of human osteoblast via PI3K pathway [22].

2.2.2. Roles and implications

The distribution of functional TRP ion channels in skeletal system interrelate both calcium ions and cytosolic calcium sensing elements closely. Studies indicate that distribution of TRPC1 and TRPC4 in bone and skeletal muscles may involve in regulating cell differentiation and osteoclast formation via modulating calcium homeostasis [16, 17], and TRPV2 can regulate osteoclastogenesis via calcium oscillations [18]. The study indicates that TRPV4 plays a role in regulating bone mass as well as mastication-associated pain at the temporomandibular joint [19, 20]. Despite studies identified that TRPV4 mutations can lead to osteoarticular pathology, the mechanism underlying TRPV4 modulation remains unclear.

2.3. TRPs in digestive system

2.3.1. Distribution patterns

To date, accumulated documentations indicate that members within four subfamilies (including TRPC, TRPV, TRPM and TRPML) of TRPs appear in digestive system. TRPC1, TRPC2, TRPC3, TRPC4, TRPC5, TRPC6 and TRPC7 are widely distributed in the stomach of mouse. TRPC1 has been detected in liver by using specific antibody [23]. For TRPC4, widely distributed in stomach, intestine and pancreas and low level in liver of human have been observed [24]. Also TRPC4 and TRPC5 have been detected in murine jejunum and colon [25]. TRPC6

has been found to distribute in smooth muscle of stomach, colon and esophagus [25, 26]. However, the roles of TRPCs within these tissues and organs are incompletely understood.

For TRPV subfamily, TRPV1, TRPV2, TRPV3 and TRPV4 are all expressed in the larynx epithelium of mice [27]. TRPV3 is found in nose, stomach, colon and small intestine in mice, especially in the epithelium of the tongue and nose. TRPV4 is expressed in stomach, small intestine and colon [28]. Other studies also revealed that TRPV4 was distributed in bile duct [29]. The murine and human TRPV6 was distributed in pancreas and gastrointestinal tract, including esophagus, stomach, duodenum, jejunum and colon [30].

Among TRPM subfamily, TRPM2 is widely expressed in several digestive organs, including stomach, intestine and low level in liver [31]. TRPM5 is found in pancreas as well as in sparse chemosensory cells located throughout the digestive track. Within the gastrointestinal system, TRPM5 was detected in the stomach, small intestine and colon, and it may regulate several physiological functions of the gastrointestinal tract. TRPM6 transcripts are detected in the intestine and colon. Furthermore, TRPM8 has been found expressed in liver [28].

The TRPMLs are all expressed in digestive system including stomach, colon, small intestine, liver and pancreas. However, the physiological roles of these distributions are still missing.

2.3.2. Roles and implications

Distributions of TRPs throughout the alimentary canal are relevant to digestive and absorptive function of mediating the whole body homeostasis of metabolism. It seems that TRPV5 and TRPV6 are involved in mediating intestinal calcium uptake and TRPM5 is involved in regulation of glucose stimulated insulin secretion [28]. TRPM2 participates in pathogenesis of bowel disease and salivary gland fluid secretion [32].

2.4. TRPs in immune system and their physiological relevance

2.4.1. Distribution patterns

In immune system, recent studies indicate broad distribution of TRPs in this system, including TRPC, TRPV, TRPM and TRPML subfamilies. Mammalian TRPC2 transcripts were detected in spleen and rat thyroid cells [33, 34]. Employing immune cells, physiological roles either of TRPC3 channels or TRPC3/6 heteromeric channel were identified to involve in Ca^{2+} signaling mechanism [35, 36]. TRPC6 was also identified in other immune cells of the lungs like alveolar macrophages [37]. Most interestingly, ovalbumin-challenged *Trpc6* knockout mice exhibited reduced allergic responses in the bronchoalveolar lavage [38]. However, the precise functional roles of TRPCs in these cells are still elusive.

For TRPVs, TRPV2 is abundantly expressed in the cells of the immune system. Study indicates that mRNA of TRPV2 was strongly expressed in the spleen [39]. TRPV2 was detected in macrophages and Kupffer cells [40]. In addition, TRPV2 was observed in mast cells [41], neutrophils [42], hematopoietic stem cells as well as both T with CD4⁺ and CD8⁺ and B with CD19⁺ lymphocytes. In hematopoietic stem cells, TRPV2 was observed with CD34⁺ [43]. TRPV4 has been detected in mast cells [44] and endolymphatic sac [45]. Meanwhile, both TRPV5 and

TRPV6 were found in lymphocytes, Jurkat leukemia T cells [46] and leukemia K562 cells [47] and may contribute to store-operated calcium entry.

Most of the TRPMs, including TRPM2, TRPM4, TRPM5, TRPM6 and TRPM7, are all expressed in the bone marrow and spleen. Specifically, TRPM2 appears in immune cells (including neutrophils, megakaryocytes, monocytes, macrophages, B lymphoblast cells, T lymphocytes, dendritic cells and mast cells). TRPM4 and TRPM6 are detected in mast cells and leukocytes, respectively [48, 49]. However, the physiological roles remain unclear.

For TRPMLs, they are all distributed in spleen and thymus of mouse. TRPML2 mRNA was detected in B cells, T cells, mastocytoma, myeloma cell lines and primary splenocytes by RT-PCR technique [50].

2.4.2. Roles and implications

Although TRPC1 has not been detected in immune system yet, but *Trpc1* deletion could reduce T helper type 2 (Th2) cells to stimuli in vivo. In vitro, proliferation and receptor-induced IL-2 production are significantly attenuated in *Trpc1* knockout splenocytes. Thus, TRPC1 may be involved in proinflammation and could be therapeutic target in immune diseases [51]. Since TRPV2 is expressed in various types of cells in immune system, it may be involved in both innate and adaptive immune responses. Moreover, TRPM2 may act as a mediator for inflammation via stimulus-induced Ca^{2+} influx in immune system, and TRPM4 in T cells may be relevant to immune response for interleukin-2 production [52].

2.5. TRPs in reproductive system

2.5.1. Distribution patterns

Based on accumulated studies so far, there are five subfamilies of TRPs distributed in the reproductive system, including TRPC, TRPV, TRPM, TRPML and TRPP. It seems that TRPCs extensively appear in reproductive system including prostate, placenta, testis, ovary, uterus, myometrium and sperm [53, 54]. Specifically, TRPC1, TRPC2 and TRPC7 are distributed in testis and sperm. TRPC3 and TRPC5 are expressed in ovary, uterus, sperm and testis. Moreover, TRPC4, TRPC7 are found in myometrium. In addition, TRPC4 is widely observed in human prostate, placenta, rat testis, ovary, human and mouse sperm. And TRPC6 is found in ovary, uterus, placenta and sperm.

All TRPVs are expressed in prostate. Specifically, TRPV1 appears in testis and prostate and TRPV2 shows in prostate. For TRPV3, it is observed in rat prostate, human placenta and testis. TRPV4 is expressed in sperm and prostate. Furthermore, TRPV5 and TRPV6 are expressed in human placenta, sperm, prostate and the epididymis. Meanwhile, TRPV4 was also detected broadly distributed in female reproductive tract [55] and oviduct [56], and these TRPV channels may function as a link between Ca^{2+} transport and Ca^{2+} signaling.

For TRPMs, all members seem to appear in prostate, testis, placenta and sperm. TRPM2 is expressed in placenta endometrium, sperm and prostate. TRPM3 is distributed in ovary, testis, sperm and prostate [57]. TRPM6 is highly expressed in testis and prostate. Moreover,

humans have strong TRPM7 expression in testis, prostate and placenta. The TRPM8 transcript was originally identified in the testis and prostate tissue [58]. In addition, TRPM8 is also expressed in human sperm.

TRPMLs are all expressed in human testis and uterus. TRPML1 is also observed in human placenta and the role is still unknown.

For TRPP subfamily, TRPP2 (*PKD2*) and TRPP3 (*PKD2L1*) transcripts were both found in many fetal and adult tissues, testis and ovary [59]. In contrast, TRPP5 (*PKD2L2*) transcription appears to be mostly restricted to the testis.

2.5.2. Roles and implications

Little is known about the roles of TRPs in reproductive system. Studies imply that TRPC2 may modulate pheromone sensory signaling transduction and TRPM8 can be a biomarker for prostate cancer.

2.6. TRPs in cardiovascular system

2.6.1. Distribution patterns

Studies have identified that five subfamilies (TRPC, TRPV, TRPM, TRPML and TRPP) of TRPs are distributed in cardiovascular system, especially in cardiomyocytes, smooth cells and endothelium cells, and these TRP ion channels may involve in hypertension as well as cardiac hypertrophy. Briefly, TRPC1, TRPC3, TRPC4, TRPC5, TRPC6 and TRPC7 are all expressed in heart of both human and mouse. Specifically, TRPC2 expression on the plasma membrane has been found in murine erythroblasts and heart [24, 60]. TRPC4, TRPC5 and TRPC7 have been observed in endothelial cells of coronary arteries [61]. The roles of these distributions are still unclear.

For TRPVs, TRPV2, TRPV4 and TRPV6 are observed in mouse heart. Specifically, TRPV1 has been found expressed in arteriolar smooth muscle [3]. TRPV2 was detected in cardiovascular system, including arterial smooth muscle cells, venous smooth muscle cells, endothelial cells and cardiomyocytes [62]. Moreover, TRPV4 was observed broadly expressed in heart as well as arteries [55].

TRPM2, TRPM3, TRPM4, TRPM6 and TRPM7 are all distributed in mouse heart. Meanwhile, all the subfamily members except TRPM8 appear in human heart. TRPM3 has been observed to express in saphenous vein, pulmonary artery, coronary artery, mesenteric artery, and femoral artery. TRPM4 was described in cardiac myocytes, vascular smooth muscle cells, vascular endothelial cells and red blood cells [62]. Furthermore, expression of TRPM8 has been reported in rat myocytes isolated from large arteries [63].

All TRPMLs are expressed in mouse heart and no relevant roles have been proved.

Both TRPP2 (*PKD2*) and TRPP3 (*PKD2L1*) are distributed in heart and the related physiological functions are still in the air to date.

2.6.2. Roles and implications

The study shows that TRPC4 and TRPC5 may regulate endothelial permeability and agonist-dependent vasorelaxation and TRPV1 could control blood flow in skeletal muscle. Moreover, TRPV2 may act as a stretch sensor and TRPM8 may involve in the regulation of vascular tone.

2.7. TRPs in urinary system

2.7.1. Distribution patterns

There are five subfamilies of TRPs appear to express in urinary system, including TRPCs, TRPVs, TRPMs, TRPMLs and TRPPs. Specifically, TRPC1, TRPC2, TRPC3, TRPC4, TRPC5, TRPC6 and TRPC7 are all expressed in kidney. Moreover, TRPC4 was found in renal epithelial cells, preglomerular resistance vessels, bladder and urothelium [64], and the specific roles are still lacking.

For TRPVs, TRPV2, TRPV4, TRPV5 and TRPV6 are all observed in mouse kidney. TRPV1, TRPV2, TRPV3 and TRPV4 were detected in bladder epithelial cells [64]. Furthermore, TRPV4 is described broadly expressed in urinary bladder and kidney [55].

Human TRPM2, TRPM3, TRPM4, TRPM5, TRPM6 and TRPM7 are all expressed in kidney, while TRPM3, TRPM4, TRPM6 and TRPM7 are found in kidney of mouse. Specifically, TRPM4 was detected in mammalian renal tubule [65], and TRPM8 has been characterized in the bladder urothelium and male urogenital tract [66].

The TRPMLs are all distributed in mouse kidney and the relevant roles are still lacking.

Both TRPP2 (*PKD2*) and TRPP3 (*PKD2L1*) are expressed in kidney and relevant roles remain unclear.

2.7.2. Roles and implications

The roles of TRPs in urinary system remain to be elucidated. TRPV1 channel was proposed to regulate bladder contractions by mediating urothelial ATP release in response to stretch [67]. TRPV2 and TRPV4 may be involved in sensing mechanical stimuli and TRPMLs could be related to urinary dysfunctions.

2.8. TRPs in respiratory system

2.8.1. Distribution patterns

Recent documented studies indicate that subfamilies for TRPC, TRPV, TRPM, TRPA, TRPML and TRPP are all distributed in respiratory system, especially in lung and other respiratory organs. Specifically, the expressions of TRPC3, TRPC6 and TRPC7 are observed in the lung of human and mouse.

For TRPVs, TRPV1, TRPV2, TRPV3 and TRPV4 are expressed in mouse respiratory epithelium. TRPV2, TRPV4 and TRPV6 are detected in lung. Specifically, TRPV1 and TRPV4 were observed in trachea and bronchi [68–70].

TRPM2, TRPM4, TRPM6 and TRPM7 are widely expressed in lung. TRPM8 with altered N-terminus has been found in human bronchial epithelial cells which localized in the endoplasmic reticulum [71].

TRPA1 was found presented in non-neuronal tissues, including human and mouse lung [72].

TRPML1, TRPML2 and TRPML3 are all distributed in the lung of mouse. While the functions related to these distribution are still lacking.

TRPP2 (*PKD2*) and TRPP3 (*PKD2L1*) are expressed in lung and the functional roles remain to be elucidated.

2.8.2. Roles and implications

The functional roles of TRPs in respiratory system need more efforts. Studies indicate that TRPC3, TRPC6 and TRPC7 may enhance respiratory rhythm regularity and TRPV1 and TRPV4 may facilitate receptor-operated calcium entry.

2.9. TRPs in endocrine system

2.9.1. Distribution patterns

Since lacking investigation employed for TRP ion channels in endocrine system, only several references for TRPs can be provided in this chapter. The expression of TRPC3 mRNA has been detected in pituitary gland [24] and the relevant roles are still unclear.

For TRPV subfamily, TRPV2 is abundantly expressed in the epithelium of the pancreatic duct, mammary gland, parotid gland and submandibular gland. Meanwhile, TRPV2 has also been detected in chromogranin-positive neuroendocrine cells in the stomach, duodenum and intestine [73]. In the pancreas, TRPV2 was found expressed in insulin-produced β -cells [74]. TRPV4 has been found in the mammary gland [75].

For TRPM subfamily, TRPM2 appears in pancreatic β -cells of endocrine system, and the channel involves in glucose-induced insulin release and cell apoptosis triggered by application of H_2O_2 [76, 77]. TRPM4 was detected to express in white and brown adipocytes [78, 79] and the roles are still missing. Recent studies reported that TRPM8 and TRPV1 are expressed in brown adipose tissues [80, 81].

2.9.2. Roles and implications

TRPs in endocrine system may be involved in sensing stimulus from cellular milieu of physical or chemical resources. Recent study shows that TRPV1 participated in the modulation of clock gene oscillations in response to light-dark cycle. Meanwhile, cold-sensing TRPM8 channel involves in the regulation of clock and clock-controlled genes and thermogenesis in brown adipose tissues [80, 81].

3. Assembly of TRP channels and its implications

TRP ion channels have been found heterogeneity in native tissues and organs due to channel subunits heteromerization. Meanwhile, wide assembly of TRP ion channel subunits of either the same subfamily or different subfamilies has been detected in heterologous expression system.

3.1. Heteromerization of TRPs with specificity

Recent investigations indicate that subunits extensively heteromultimerize in the TRPC subfamily. Accordingly, the overlapped distribution patterns of TRPC proteins in the hippocampus and peripheral tissues are also coincident with the heteromerization. Specifically, formation of heteromeric complexes by both TRPC5 and another member of the same subfamily, TRPC4, with the TRPC1 subunit (TRPC1/5 and TRPC1/4) has been identified in mammalian cells. Using quantitative high-resolution mass spectrometry, TRPC1, TRPC4 and TRPC5 were demonstrated to assemble into heteromultimers with each other in the mouse brain and hippocampus [82]. In HEK293 cells, cotransfection of TRPC1 and TRPC4 yielded novel nonselective cationic channels. Heteromeric TRPC1/4 channel showed dynamic gating property depending on TRPC1 isoform subtypes and receptor stimulation system. [83]. Using GST pull-down assays, heteromerization of TRPC1 with TRPC3 was examined and the ankyrin repeats (AR) region of TRPC3 could mediate the heteromeric TRPC1/3 formation. Furthermore, the heteromeric TRPC1/3 may participate in regulating the resting cytosolic Ca^{2+} levels in skeletal muscle [84]. Coassembly of TRPC1 and TRPC5 in hippocampal neurons and in HEK293 cells resulted in a novel nonselective cation channel with a voltage dependence similar to NMDA receptor channels. Similar associations were reported between TRPC1 and TRPC3 via an N-termini domain interaction in salivary gland cells. In addition, heteromerization of TRPC3 and TRPC4 seems to produce channels with a distinct pore structure clearly different from those of the homomeric TRPC3 and TRPC4 channels. Moreover, study also revealed that TRPC1/3/7 can interact to form a store-operated channel complex [85].

For TRPV subfamily, using fluorescence resonance energy transfer (FRET) as well as single-channel recording, widespread interaction between any two members of TRPV1–4 has been identified [86]. This study provided evidence that thermosensitive TRPV channel subunits can form heteromeric channels with intermediate conductance levels and gating kinetic properties compared to homomeric channels. Moreover, colocalization and association between TRPV1 and TRPV2, TRPV1 and TRPV3 as well as TRPV5 and TRPV6 can form heteromeric channel complexes. Recent study identified that TRPV4 could facilitate with TRPV1 in some sensory neurons [87].

Heteromerization of TRPM subunits remains far less clear. Association between TRPM6 and TRPM7 formed heteromeric channels with intermediate conductance and gating properties. Recent study uncovered heteromeric TRPM6/7 channels with altered pharmacology and sensitivity to intracellular Mg-ATP compared with homomeric TRPM7. Furthermore, TRPM6 kinase domain modulated heteromeric channel sensitivity of intracellular Mg-ATP concentrations [88].

The mucolipin TRPML family exhibited low similarity to other TRPs. Montell and coworkers demonstrated that TRPMLs can assemble to form heteromultimers with intermediate

conductance and kinetic properties. Moreover, the presence of either TRPML1 or TRPML2 specifically modulates TRPML3 trafficking from endoplasmic reticulum to lysosomes [85].

3.2. Assembly of TRPs in different subfamilies

Extensive studies revealed widespread heteromerization within the mammalian TRP channel superfamily. Heteromeric TRPP2/TRPC1 channel complexes with a stoichiometry of 2:2 exhibited a new receptor-operated channel property. TRPP2 selectively assembled with TRPC1 and TRPC4 to form channel complexes mediating angiotensin II-induced Ca^{2+} responses in mesangial cells. Heteromeric cation channels composed of the TRPP2 mutant and the TRPC3 or TRPC7 protein enhanced receptor-activated Ca^{2+} influx that may lead to dysregulated cell growth in autosomal dominant polycystic kidney disease. Using coimmunoprecipitation, the composition of TRPP2/TRPC5, TRPP3/TRPC1, TRPP3/TRPC5, TRPP5/TRPC1 and TRPP5/TRPC5 was also identified. TRPP2 and TRPV4, which formed heteromeric channel complex, have been reported both in vivo and in vitro. Then, heteromeric TRPP2/TRPV4 complex with a 2:2 stoichiometry and alternating subunit arrangement was identified using atomic force microscopy approach [85]. The study indicates that TRPV4 could form heteromeric channels with TRPC1 in vascular endothelial cells. Then, Ca^{2+} store depletion enhanced the trafficking of TRPV4/TRPC1 channels into the plasma membrane, thus contributed to mediate store-operated current and store-operated calcium ion entry [89]. TRPV4 can form a heteromeric channel with TRPC6 in the pulmonary artery smooth muscle cell, and TRPV4 plays a critical role in hypoxic pulmonary vasoconstriction potentially via cooperation with TRPC6 [90]. TRPV6 exhibited substantial colocalization and in vivo interaction with TRPC1, and functional interaction of TRPV6 with TRPC1 negatively regulates Ca^{2+} influx in HEK293 cells [91]. Heteromeric TRPV5 and TRPML3 channels with novel conductance were detected under conditions that did not activate either TRPML3 or TRPV5 [92].

Moreover, novel combination of TRPC1/TRPC6/TRPV4 may mediate mechanical hyperalgesia and primary afferent nociceptor sensitization. Subsequently, TRPV4, TRPC1 and TRPP2 have been reported to form a flow-sensitive heteromeric channel in primary cultured rat mesenteric artery endothelial cells as well as HEK293 cells. Moreover, heteromeric TRPV4/TRPC1/TRPP2 channel can mediate the flow-induced Ca^{2+} increase in native vascular endothelial cells [93].

3.3. Assembly between TRPP channels and receptor-like polycystin-1 family proteins

PKD1 and PKD2 have been identified as the genes mutated in autosomal dominant polycystic kidney disease (ADPKD). The TRPP ion channel subfamily (PKD2-like group) contains three members of TRPP2 (PKD2), TRPP3 (PKD2L1) and TRPP5 (PKD2L2). The receptor like polycystin-1 family proteins (PKD1-like group) contains five members, including PKD1, PKDREJ, PKD1L1, PKD1L2 and PKD1L3. TRPP subunits not only assemble into functional homomeric ion channels but also assemble with polycystin-1 family members to form heteromeric receptor-channel complexes.

Heteromeric interaction between TRPP2 and PKD1 has been identified by several groups throughout the past decade. TRPP3 can also interact with PKD1, and the interaction is essential for TRPP3 trafficking and channel formation. Along these lines, studies also showed that TRPP3

and PKD1L3 colocalized in taste receptor cells. Heteromeric complex with three TRPP3 and one PKD1L3 functions as an acid sensor. Single amino acid mutations in the putative pore region of both proteins alter ion selectivity of the channel. A TRPP3 C-terminal coiled-coil domain forms a trimer in regulating assembly and surface expression of the TRPP3/PKD1L3 complex [94]. Moreover, heteromeric TRPP3/PKD1L3 channel complex in mice and humans regulated translocation and expression of hedgehog pathway proteins through modulation of ciliary calcium concentration [95]. Recent study found that extracellular loops between the first and second transmembrane segments of TRPP2 and TRPP3 associated with the extracellular loops between the sixth and seventh transmembrane segments of PKD1 and PKD1L3, respectively, and the associations between these loops are essential for the trafficking and function of the complexes [96].

3.4. Implications of assembly of TRPs

It is clear that coassembly of ion channel subunits yields a variety of diverse channel complexes. Heteromultimerization among mammalian TRP subunits produces novel channel types with functional properties distinct from their homomeric counterparts. Heteromerization of mammalian TRPV1/3, TRPV5/6, TRPML1/2, TRPC1/3, TRPC1/4, TRPC1/5, TRPC3/4, TRPC4/5, TRPV5 and TRPML3 has been identified to produce channels with novel or altered properties.

Meanwhile, TRPP2 coassembled with TRPC1 to form heteromultimeric channels that exhibit new receptor-operated property implicated in mechanosensation. Furthermore, association between TRPP2 and TRPV4 produces a channel with mechanosensitive and thermosensitive roles. Recent study indicates that heteromultimers of TRPC1/4, TRPC1/5 and TRPC4/5 in the mouse brain and hippocampus involved in regulation of spatial working memory and flexible relearning by facilitating proper synaptic transmission [82]. TRPC1 and TRPC6 with TRPV4 are frequently coexpressed in DRG neurons; TRPC1 and TRPC6 subunits are incorporated with TRPV4 to mediate mechanical hyperalgesia and primary afferent nociceptor sensitization. Interestingly, TRPV4 is required for itch signaling in some sensory neurons via facilitation of TRPV1. The formation of heteromeric complexes could be a prevalent mechanism by which the vast array of somatosensory information is encoded in sensory neurons [87]. In addition, functional interaction between the noxious cold-sensitive TRPA1 channel subunit and the noxious heat-sensitive TRPV1 channel subunit could contribute to TRPA1-mediated responses in trigeminal sensory neurons. Moreover, colocalization of PKD1L3 with TRPP3 (PKD2L1) in taste receptor cells may involve in taste sensory transduction. In summary, heteromerization of TRPs to novel channel complexes extends TRP channel distribution and function.

4. Discussion

4.1. More distribution relevance of TRPs need to be fully elucidated

TRP ion channels are almost expressed in all types of mammalian cells and their functions are also diverse as their distributions in tissues and organs. TRP channels not only act as polymodal cellular sensors, which are involved in cellular sensing from somatosensation, hearing, taste and olfaction [14], but also participate in many other physiological and pathological

process from metabolism, homeostasis and even carcinogenesis. To date, the puzzle of relevant roles regarding TRP distribution in tissues and organs remains incompletely understood.

Specifically, the functions of TRPCs in mammalian are involved in temperature perception, mechanosensation, proinflammation, pheromone modulation, vasorelaxation as well as respiratory rhythm regulation. Furthermore, they also regulate cell differentiation and bone mass via calcium involving. However, the distribution relevance of TRPs in digestive as well as urinary system needs more and deeper investigation.

For TRPVs, the distribution relevance is mostly related to somatosensation such as thermosensation, mechanosensation and nociception [1]. Meanwhile, TRPVs distribution also acts as sensory channels for receptor-operated calcium entry. But the related roles in immune system, urinary system as well as respiratory system remain elusive.

The subfamily of TRPM is extensively distributed in nervous system, skeletal system, digestive system, immune system, reproductive system, cardiovascular system, urinary system, respiratory system and endocrine system. Their functions are involved in warm or cold perception as well as thermogenesis, auditory mechanoreception, taste, metabolism, vascular tone regulation and inflammation. In addition, TRPM8 can be a biomarker for carcinogenesis of prostate. Further investigations regarding functional relevance of TRPMs' distributions need to be deeply elucidated, in particular in urinary system as well as respiratory system.

TRPA1 is mostly expressed in nervous system. Its functions involve in thermosensation, auditory mechanosensation as well as olfactory transduction. Meanwhile, TRPMLs are expressed in brain, heart, kidney and lung. Moreover, they appear in digestive system, immune system and reproductive system. But the relevance of the distribution is still missing. Little is known about the related roles of TRPPs in reproductive system, cardiovascular system, urinary system and respiratory system.

Despite TRPs have been explored extensively for almost half of century, our understanding of the implications related to TRPs distribution is still missing a lot of pieces. Further investigation regarding this relevance needs to be elusive urgently.

4.2. Heteromerizations tangle the elucidation for distributions and functions

The intracellular distributions of TRP ion channels may be dynamically regulated by cytosolic changes. However, little is known about whether and how TRP channels change subunit composition in response to environmental stimuli. So far, most published studies focused on the static TRP ion channels subunit composition. How does the cell determine how and when subunits are coassembled? To what extent does extra or intracellular milieu affect the molecular sensitivity of the neuron? In fact, the coassembly of TRP ion channel subunits in living cells is dynamically regulated. Studies indeed sustain that the distribution of TRP ion channel in cells changes dramatically upon stimulation [97, 98]. Thus, when we study the distribution and function of TRPs, the dimension for dynamic influences has to be considered.

Furthermore, the extensive studies focus on TRP ion channels heteromerization, while much remains to be elucidated about the physiological consequences of heteromultimerization

among TRP subunits. Practical approach and advanced technique to monitor assembly of dynamic TRP ion channel subunits should be explored. Moreover, distribution of heteromeric TRP complexes involving in physiological and pathophysiological processes calls for more solid and careful investigations.

5. Conclusions and outlook

In this chapter, we described our understanding in distribution and assembly of TRP ion channels based on recent references. Haboring a superfamily of ion channels protein, TRPs exhibit ubiquitously distributions in mammals which depict a diverse and fascinating network. This makes the investigation more painstaking for grasp both the correct expression pattern and the roles of these TRPs. With recent technological advances of gene sequencing combines high throughput screening, breakthrough in this area will be likely achieved. Moreover, reporter genes as well as high resolution technique provide more precise location of where the TRPs really are.

Understanding TRPs from distribution to assembly not only help us to comprehend the physiological roles of TRPs but also can widen the perspective of taking TRPs as potential therapeutic targets with their pathological relevance.

Although many aspects have been deciphered through focused studies regarding TRP ion channels expression and assembly during past decades, our knowledge on the implication of TRPs distribution and assembly remains limited. There are still gaps and bewildered controversies in our understanding of these TRPs. The whole scope of TRP distribution and assembly needs more thorough and scrutinized investigation, and new technical approach applied for TRP channel investigations needs to be developed.

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Conflict of interest

No competing financial interests exist.

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