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Transient Receptor Potential Channels

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Dedicated to the living memory of my mother
Sayera Khatun

Preface

During a conference titled "TRP channels, from sensory signaling to human disease", held at the Karolinska Institute, Stockholm, Sweden, on 26th and 27th September, 2009, I was contacted by Springer to publish the proceedings of the conference. After some discussion with some of the speakers, I understood that that was not going to happen. In stead, we were happy to publish a short meeting report [1]. I thought, the excitement and the momentum that resulted from the conference could be utilized in compiling a substantial book rather than a modest conference proceeding. The idea for a TRP book appeared very timely. This field of research has progressed fast and a few books on the TRP channels that have been published before have become outdated. My immediate concern was whether I would have enough time for editing another book. From a previous book "The Islets of Langerhans" (http://isletbook.islets.se), I knew that for completing a book, it requires a lot more time and energy than one anticipates at the onset [2]. But my real fear was whether I am the most appropriate person to edit a book on the TRP channels. After all, it is a vast and expanding field dominated by a handful of eminent electrophysiologists and biophysicists. When it comes to the TRP channels, I am at best an enthusiast and by no means an expert. I tried to adopt co-editor(s) but the ones I approached were already over committed. My other concern was whether people read books these days as they used to do in the past; books are, after all, less dynamic than journals and on-line publications. It took me some time, to overcome these perplexing thoughts, and then there was only one thing left for me to do, i.e., to take the idea of this new book on TRP channels to completion as fast and as best as possible at any cost.

During the first few weeks, it became pretty obvious to me that many scientists prefer to spend their time in publishing original papers in high-impact journals rather than in writing book chapters especially if they are not paid any remuneration for their contribution. In most academic environments, a short report in a high-impact journal counts more than an extensive and useful chapter in a book, which, often do not have any impact factors. I wrote to many scientists who have published something on TRP channels in any journal. I contacted scientists whom I knew or whom I met personally. In the end, I was rather overwhelmed that so many authors agreed to contribute a chapter in his book. The enthusiasm among the

authors was noticeably high. My communication with the authors and the referees was fast, smooth, informal, and very satisfying. All authors finally submitted their respective chapters in time. The only chapter that was delayed was mine, a privilege and a problem of being the editor.

In this book one will find diverse information on the TRP channels starting from some of the essential background information to some of the cutting edge researches, from some of the most established facts to some of the most hotly debated issues of our time, and from the structural biology of the channels to the molecular basis of some human illnesses. But it is by no means an encyclopedia. The emphasis was not on making the book as complete as possible but on making the best use of the competence and interests of the authors who agreed to contribute. Some important topics are missing from the book simply because I could not persuade anyone to contribute on those topics. The authors enjoyed enormous freedom in choosing the contents of their respective chapters and in structuring the chapters as they wished. In some instances, more than one chapter was dedicated to somewhat overlapping topics to ensure that different views of different authors can be accommodated in the same book. Many authors have included their own ideas, views, and speculations which can form the basis for new testable hypotheses for future research. In this book there is something for everyone, both for the beginners and for the experts. But it is important that the readers treat the contents of this book just as starting points, question everything that they read in this book and actively find their own answers through further research.

I am grateful to all the authors and the co-authors, who, in spite of their heavy preoccupation with numerous other activities and deadlines, have worked hard to make their chapters as best as possible within the limited time that they were allotted. When I learnt from several authors that the reasons for delay of their chapters were unexpected personal or family situations or bereavement of a family member, then I paused and reflected; life is not just a bundle of papers. I would like to thank all the referees who have taken time to really read the manuscripts and to come up with very useful comments. The most important thing that I have enjoyed and I have benefited from is the reading of the comments of many referees and the authors' replies to these comments. I wish I could include some of the referees' comments in this book. In spite, of all our efforts, I am worried that the book contains many mistakes that we were not aware of. I will be grateful if readers point out such mistakes and post their comments on the website of the book: http://trpbook.islets.se. This will make the book a bit more dynamic and we all will have opportunity to learn from the mistakes.

I believe we shall all be happy, if this book can further intensify research in the field of the TRP channels in the context of understanding human physiology and pathogenesis of human diseases. Let research in this field confer some of the greatest benefits on mankind. Thanks to Karolinska Institutet that has provided the infrastructure for my academic activities over past two decades. Thanks to Melania Ruiz and Ilse Hansen for handling the practical aspects of handling the chapters and rest of the book. This editorial was written on board a high speed train that symbolizes the fast speed of research in the TRP field.

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Chapter 1
Structural Biology of TRP Channels

Minghui Li, Yong Yu, and Jian Yang

Abstract Structural studies on TRP channels, while limited, are poised for a quickened pace and rapid expansion. As of yet, no high-resolution structure of a full length TRP channel exists, but low-resolution electron cryomicroscopy structures have been obtained for 4 TRP channels, and high-resolution NMR and X-ray crystal structures have been obtained for the cytoplasmic domains, including an atypical protein kinase domain, ankyrin repeats, coiled coil domains and a Ca^{2+}-binding domain, of 6 TRP channels. These structures enhance our understanding of TRP channel assembly and regulation. Continued technical advances in structural approaches promise a bright outlook for TRP channel structural biology.

1.1 Introduction

Full understanding of ion channel function requires high-resolution three-dimensional (3D) structures. Structural studies on ion channels entered a new phase in 1998 after the publication of the crystal structure of the bacterial K^+ channel, KcsA [1]. Since then, there has been a rapid growth in the number of ion channel structures. To date, there are ~90 crystal structures of full length or near full length ion channels, ~50 electron microscopy structures of full length or near full length ion channels, and ~130 crystal and nuclear magnetic resonance (NMR) structures of ion channel fragments. These structures have led to a quantum leap in our understanding of the molecular and biophysical mechanisms of ion channel assembly, selectivity, conduction, gating and regulation.

TRP channels constitute a distinct superfamily of ion channels and are distantly related to voltage-gated K^+, Na^+ and Ca^{2+} superfamilies. They are expressed and function in diverse organisms, including yeasts, worms, fruit flies, mice and humans. Excluding yeast TRPs, there are seven subfamilies: TRPC, TRPV, TRPM, TRPA,

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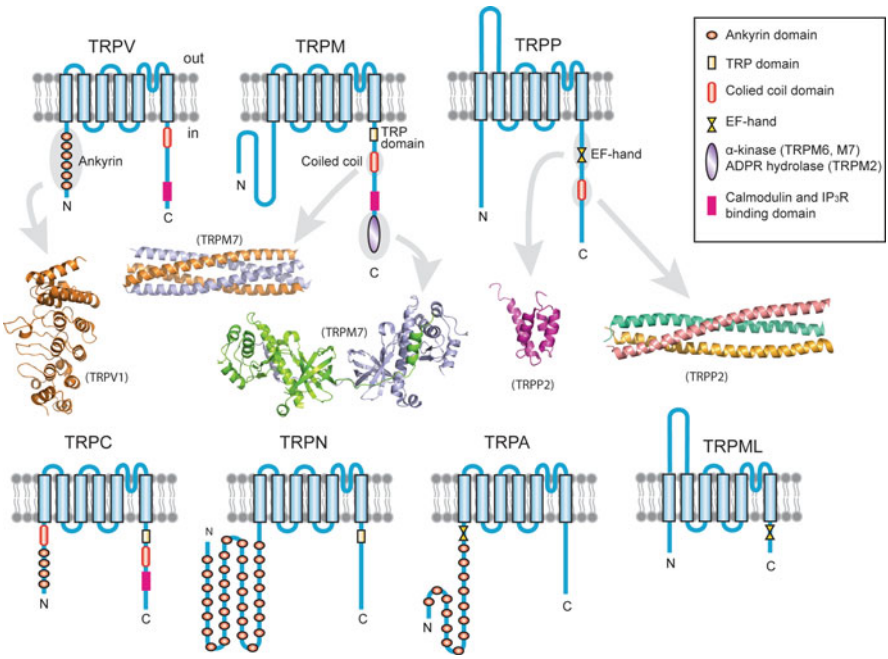

Fig. 1.1 TRP channel subfamilies and the transmembrane topology and domain organization of their subunits. Only commonly present and readily identifiable domains or motifs in the cytoplasmic N and C termini are indicated. Examples of high-resolution structures of some domains or motifs are presented

TRPN, TRPP and TRPML, with TRPN absent in mice and humans (Fig. 1.1) [2]. Each subfamily has one or more members. Mice have a total of 28 different members, and humans 27. All TRP channel subunits have six putative transmembrane segments and a pore-forming loop between the last two transmembrane segments (Fig. 1.1). The amino (N) and carboxyl (C) termini are located intracellularly and vary vastly in length (Table 1.1) and amino acid (aa) sequence. These cytoplasmic regions contain various well-recognized domains and motifs that are likely involved in channel assembly, activation and regulation through protein–protein and/or protein–ligand interactions (Fig. 1.1).

All TRP channels are cation selective, with some being highly selective for Ca^{2+} or Mg^{2+} [2]. In accord with their amino acid sequence diversity, TRP channels exhibit varied activation and modulatory mechanisms, such as stimulation of G protein coupled receptors, extracellular and intracellular ligands (including H^+, Ca^{2+} and Mg^{2+}), phosphoinositide-4,5pbisphosphate (PIP_2), temperature, and mechanical stretch [2]. To fully understand TRP channel diversity, function and regulation, it is necessary to gain structural information on different types of TRP channels.

Of the existing ion channel structures, most come from K^+ channels. This is due, in part, to their vast variety and their existence in bacteria, which make them more tractable to structural approaches, especially X-ray crystallography, because they

Table 1.1 Predicted region and length of the cytoplasmic N and C termini of TRP channel subunits and the number of low-complexity residues in these regions

	N terminus			C terminus		
Protein	Channel region	# of residues	# of low-complexity residues	Channel region	# of residues	# of low-complexity residues
TRPC1	1–316	316	14	610–759	150	0
TRPC2	1–626	626	92	918–1,172	255	82
TRPC3	1–351	351	0	671–848	178	0
TRPC4	1–327	327	38	618–977	360	21
TRPC5	1–327	327	41	622–973	352	56
TRPC6	1–404	404	22	726–931	206	7
TRPC7	1–351	351	11	671–862	192	0
TRPV1	1–433	433	0	681–839	159	0
TRPV2	1–390	390	0	645–764	120	0
TRPV3	1–438	438	56	675–790	116	0
TRPV4	1–468	468	26	716–871	156	0
TRPV5	1–326	326	0	577–729	153	22
TRPV6	1–326	326	16	577–725	149	10
TRPM1	1–760	760	84	1,053–1,533	481	27
TRPM2	1–750	750	40	1,046–1,503	458	26
TRPM3	1–716	716	59	955–1,554	600	34
TRPM4	1–687	687	43	1,041–1,214	174	34
TRPM5	1–643	643	0	975–1,158	184	0
TRPM6	1–742	742	15	1,075–2,022	948	34
TRPM7	1–756	756	15	1,102–1,864	763	13
TRPM8	1–692	692	16	977–1,104	128	24
TRPML1	1–69	69	12	518–580	63	13
TRPML2	1–61	61	0	508–566	59	0
TRPML3	1–66	66	13	503–553	51	0
TRPP2	1–224	224	99	681–968	288	87
TRPP3	1–104	104	15	558–805	248	22
TRPP5	1–33	33	0	492–613	122	12
TRPA1	1–717	717	0	962–1,119	158	0

All amino acid sequences are from humans except TRPC2, which is from mice, as human *TRPC2* is a pseudogene. Transmembrane helices were predicted using the TMHMM Server v. 2.0 at http://www.cbs.dtu.dk/services/TMHMM/. Low-complexity sequences were predicted using the program SEG [80] with the default settings.

can be more abundantly expressed, are more stable, and hence, are more amicable to purification and crystallization. TRP channels, however, are not endogenously expressed in bacteria. This is perhaps a major contributing factor in the present lack of even a single high-resolution structure of any full length TRP channel. Nevertheless, low-resolution structures have been obtained for 4 full length TRP channels by electron microscopy (EM). Meanwhile, X-ray crystallography and NMR spectroscopy have been employed effectively to garner high-resolution structures of functionally important cytosolic domains of 6 TRP channels (Table 1.2). This chapter describes the existing TRP channel structures and, when available,

Table 1.2 High-resolution structures of TRP channel fragments

Structural description	Channel region	Species	Resolution	Method	PDB code	References
TRPM7 α-kinase	1,549–1,828	Mouse	2.8 Å	X-ray crystallography	1IAJ	[27]
TRPM7 α-kinase, with AMP·PNP	1,549–1,828	Mouse	2.0 Å	X-ray crystallography	1IA9	[27]
TRPM7 α-kinase, with ADP	1,549–1,828	Mouse	2.4 Å	X-ray crystallography	1IAH	[27]
TRPV1 ankyrin repeats	101–364	Rat	2.7 Å	X-ray crystallography	2PNN	[39]
TRPV2 ankyrin repeats	75–326	Rat	1.65 Å	X-ray crystallography	2ETB	[37]
TRPV2 ankyrin repeats	69–319	Human	1.7 Å	X-ray crystallography	2F37	[40]
TRPV4 ankyrin repeats	133–382	Chicken	2.3 Å	X-ray crystallography	3JXI	[38]
TRPV6 ankyrin repeats	44–265	Mouse	1.7 Å	X-ray crystallography	2RFA	[41]
TRPM7 coiled coil	1,230–1,282	Rat	2.01 Å	X-ray crystallography	3E7K	[57]
TRPP2 coiled coil, long	833–895	Human	1.9 Å	X-ray crystallography	3HRN	[58]
TRPP2 coiled coil, short	833–872	Human	1.9 Å	X-ray crystallography	3HRO	[58]
TRPP2 E-F hand	724–796	Human		NMR	2KLE	[74]
TRPP2 E-F hand	720–797	Human		NMR	2KQ6	[75]

the mechanistic insights they provide, beginning with a brief overview of structural approaches and considerations. Advances in TRP channel structural biology have been covered in several recent reviews [3–7].

1.2 Structure-Determination Methods and Considerations

When examining the structure of a protein or a protein complex, the first and foremost concern is its resolution. At nanometer-resolutions, certain general features of the protein can be ascertained, including its shape, dimension, subunit stoichiometry

and domain organization (Fig. 1.2a). At 4- to 9-Å resolutions, secondary structures can be discerned (Fig. 1.2b). At resolutions below 3.7 Å, amino acid side-chains can be visualized and assigned – the higher the resolution, the higher the precision and confidence (Fig. 1.2c). For example, aromatic side-chains can be identified at 3.5 Å, and individual atoms can be resolved at 1.5 Å [8].

Three methods are commonly used to determine protein 3D structures – electron cryomicroscopy (cryo-EM), NMR spectroscopy and X-ray crystallography. These methods have different applications, advantages and disadvantages, especially when applied to integral membrane proteins.

Cryo-EM can be used to determine the structure of proteins of various shapes, forms and sizes [9–11]. It is particularly useful for proteins that are too large or too difficult for NMR and X-ray crystallography. Moreover, cryo-EM can probe proteins in their native lipid environment. Cryo-EM can be used to visualize proteins in two-dimensional (2D) sheets or helices or in non-crystal forms. The resolution of single-particle cryo-EM, the most widely used cryo-EM method, generally ranges from 30 to ~6 Å, depending on the quality of protein preparation, protein symmetry,

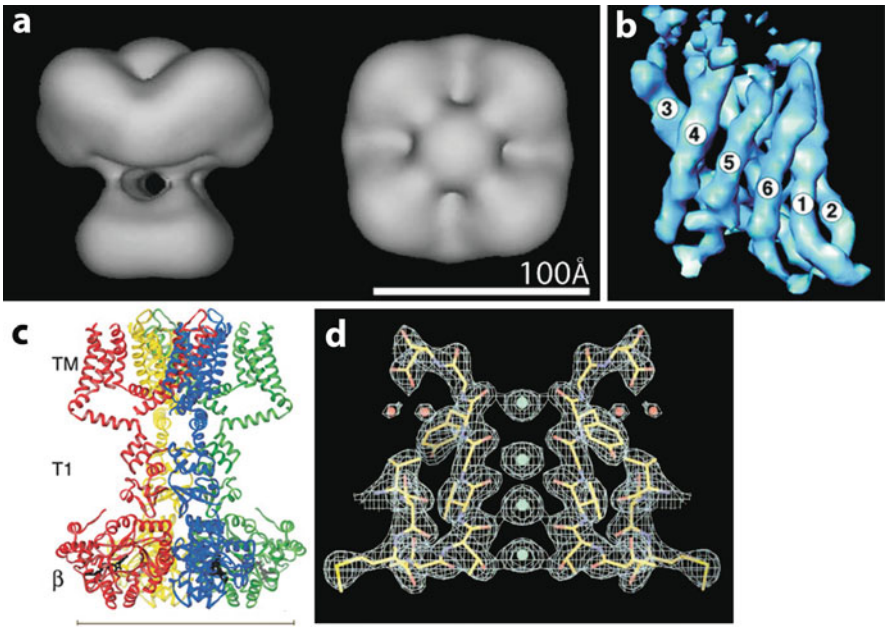

Fig. 1.2 Examples of membrane protein structures at different resolutions. (**a**) Side view (*left*) and top view (*right*) of a cryo-EM structure of the *Drosophila* Shaker K^+ channel at 25 Å resolution, revealing a fourfold symmetry and a two-layered architecture [76]. (**b**) Side view of the structure of a monomer of aquaporin 1 obtained by 2D cryo-EM at 6 Å resolution, revealing 6 distinct tilted rods that correspond to membrane-spanning α helices [77]. (**c**) X-ray crystal structure of the rat $K_v1.2$ channel at 2.9 Å resolution (*left*, PDB code 2A79) [78] and (**d**) The electron density map and side chain assignment of the ion selectivity filter of a rat $K_v1.2$–$K_v2.1$ chimeric channel at 2.4 Å resolution (*right*, PDB code 2R9R) [79]

sample size, data processing, and reconstruction. Near atomic resolution can be obtained for highly symmetrical complexes (see e.g., [12]). With 2D crystals, cryo-EM can achieve atomic resolution. For example, the structure of aquaporin-0 in double-layered 2D crystals has been determined at 1.9 Å [13], the highest resolution protein structure solved to date by cryo-EM.

Both NMR and X-ray crystallography allow the determination of protein structures at atomic resolutions. NMR is mainly applicable to relatively small proteins or protein fragments, usually less than 25 kDa, for structural determination, though technical advances allow proteins of up to 900 kDa to be studied [14]. Also, both soluble and membrane proteins can be examined [14, 15]. For partially or wholly unstructured proteins or protein fragments that are resistant to crystallization, NMR is often the only method for structural determination.

X-ray crystallography is by far the most widely used and most effective structure-determination method. As of March 2010, ~86% of the protein structures deposited in the Protein Data Bank and ~88% of the ion channel structures (full length and fragments) are solved by X-ray crystallography. The number of unique structures of membrane proteins solved by X-ray crystallography has been increasing exponentially, from a total of 25 in 1998 when the KcsA structure was published to 212 in 2009. Despite its power, X-ray crystallography has limitations, especially when applied to membrane proteins. Major challenges include maintaining the protein in a soluble form and in its native oligomeric state, crystallizing the protein, and achieving atomic resolution.

An important consideration in protein structure determination is the expression system. Four types of cells have been routinely employed to overexpress membrane proteins: bacteria (*Escherichia coli*), yeast (*Saccharomyces cerevisiae* and *Pichia pastoris*), insect cells (Sf9 cells), and mammalian cells (HEK293 cells and COS7 cells). Obviously, proteins that are endogenously expressed in bacteria are likely to yield better expression in *E. coli*. There are yet no well-defined guiding principles in choosing an expression system for vertebrate membrane proteins. Trial-and-error seems to be the most effective strategy.

Another key consideration is the choice of detergents. Membrane proteins are embedded in lipids and thus require detergents for solublization, purification and crystallization [16, 17]. Nonionic and zwitterionic detergents are generally less harsh on proteins than ionic detergents and have been much more successfully utilized in structural investigation. Commonly used nonionic and zwitterionic detergents include n-decyl-β-D-maltoside (DM), n-dodecyl-β-D-maltoside (DDM), lauryldimethylamine-N-oxide (LDAO), n-octyl-β-D-glucoside (OG), dodecyl octaethylene glycol ether (C12E8), and 3-[(3-cholamidopropyl)-dimethylammonio]-1-propane sulfonate (CHAPS). In general, detergent concentrations should be significantly higher than the critical micelle concentration (CMC), the concentration at which detergent monomers aggregate to form micelles. Sometimes, different detergents are used for solublization and for purification and crystallization. As with choosing the expression system, there is not a set of rules regarding detergent choice and the concentration to be used; they are largely determined empirically.

Yet another critical consideration is whether to work on full length proteins or smaller fragments. From the functional point of view, it is obviously more desirable to obtain the structure of full length proteins. With cryo-EM, this is usually achievable, even for very large proteins. This is, however, not often feasible with X-ray crystallography. To facilitate protein expression, purification, crystallization, and to improve resolution, it is often necessary to remove parts of a protein. Even with such maneuvers, it is still often unattainable to solve the structure of a membrane protein. In such cases, an alternative is to obtain the structure of the soluble domains of the protein. The extracellular and intracellular regions of membrane proteins usually contain functionally important domains and motifs, which often fold into compact and defined structures. These domains and motifs often can be independently expressed, purified and crystallized, and their structures can provide useful insights into the workings of a protein. Still, the extracellular and intracellular regions of ion channel proteins, including TRP channels, often contain low-complexity sequences (Table 1.1), which are generally detrimental to structural determination by both NMR and X-ray crystallography [18]. Thus, even when working with channel fragments, it is usually necessary to trim them further. Indeed, none of the available high-resolution structures of TRP channels comes from a full length N or C terminus (Table 1.2). Finally, it should be cautioned that the structure of an isolated protein fragment may not always represent its structure in the intact protein. Thus, the validity and usefulness of such a structure needs to be tested in the full length protein.

1.3 EM Structures

Low-resolution (15–35 Å) EM structures have been obtained for 4 TRP channels from 3 different subfamilies: TRPM2, TRPC3, TRPV1 and TRPV4 (Fig. 1.3) [19–22]. The structures of the latter 3 channels were determined by cryo-EM, but that of TRPM2 was determined by EM with negative staining. A common feature of all four structures is that they exhibit a fourfold rotational symmetry, consistent with the tetrameric subunit stoichiometry that has been demonstrated for several TRP channels by other methods [23, 24]. Strikingly, while the general structure of TRPV1 and TRPV4 is similar, that of TRPM2 and TRPC3 is markedly different (Fig. 1.3).

The structure of rat TRPV1 was determined by single particle cryo-EM at 19 Å resolution (Fig. 1.3a) [21]. The reconstructed 3D structure stands ~150 Å high and contains two interconnected regions. The small region measures ~60×60 Å, with a height of 40 Å, and accounts for ~30% of the total mass. It likely corresponds to the transmembrane portion of the channel, as suggested by its relative mass and a reasonable fit of the high-resolution structure of the transmembrane domains of the $K_v1.2$ K^+ channel into this region. The large region is shaped like a basket, with a central cavity, and is connected to the small region by 4 bridges. This region, comprising ~70% of the total mass, is ~100 Å wide and 110 Å high and

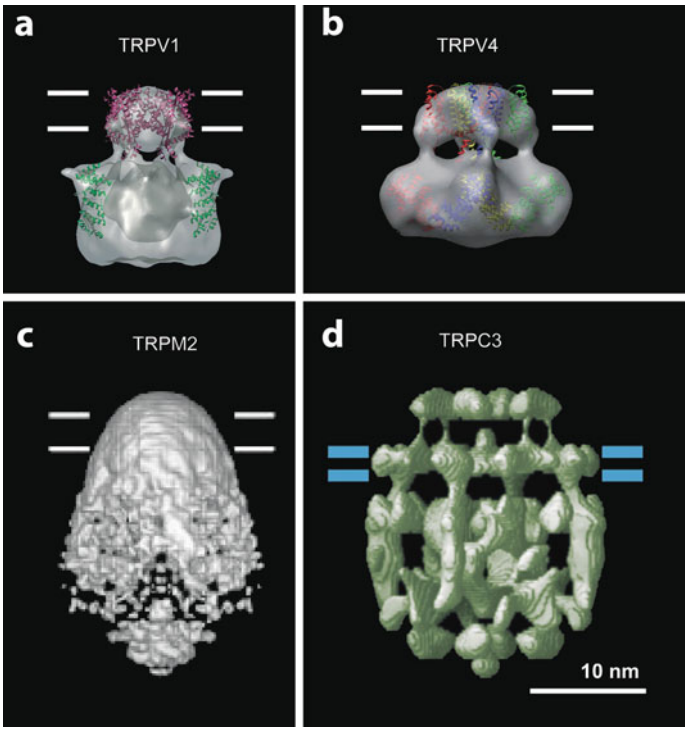

Fig. 1.3 TRP channel EM structures. (**a**) Cryo-EM structure of TRPV1 [21], superimposed with the crystal structure of the $K_v1.2$ transmembrane domains (*maroon*; PDB code 2A79) and of the ankyrin repeat domain of TRPV1 (*green*; PDB code 2PNN). (**b**) Cryo-EM structure of TRPV4 [22], superimposed with the crystal structure of Mlotik1 (*top*; PDB code 3BEH) and of the ankyrin repeat domain of TRPV1 (*bottom*). (**c**) EM structure of TRPM2 with negative staining [19]. (**d**) Cryo-EM structure of TRPC3 [20]. All structures are side-views. The *white lines* mark putative transmembrane regions, so do the *blue lines*, as presented in [20]. The resolutions of all four structures are based on the 0.5 cutoff criterion in the Fourier shell correlation

probably corresponds to cytoplasmic N and C termini. Indeed, the 6 ankyrin repeats present in the N terminus of TRPV1 can be comfortably fitted into this region in the vertical orientation. The functional importance of the vacant central chamber is unknown.

The structure of rat TRPV4, reconstructed to 35 Å resolution, is similar to that of TRPV1 and shares the two-layered general architecture (Fig. 1.3b) [22]. This is consistent with the similar size of the two channels (rat TRPV1 and TRPV4 subunits contain 838 and 871 amino acids, respectively). The small region accounts for 30% of the total volume and has a dimension of ~85 Å. The transmembrane domains of Mlotik1, a prokaryotic K^+ channel, can be largely superimposed onto this region. The large region is ~112 Å wide, and as in TRPV1, is linked to the putative transmembrane region through 4 short bridges. The N terminus of TRPV4