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Bernd Nilius
Veit Flockerzi *Editors*

Mammalian Transient Receptor Potential (TRP) Cation Channels

Volume I

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Mammalian Transient Receptor Potential (TRP) Cation Channels

Volume I

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Preface

When we edited in 2007 the first issue on transient receptor potential channel in the Handbook of Experimental Pharmacology, we were all very excited by the progress in this field although only one decade after cloning the first TRP channel had passed. At this time, somewhat less than 5,000 papers were published on TRP channel (1/1/1960 until 31/12/2006). If we check now the period (1/1/2007 until 13/1/2014), additional 9,300 papers can be found in a PubMed search.[1] Needless to say, the general interest on these 28 members of the Trp gene family which encode ion channels is nearly exponentially growing. Therefore, it seemed to be indicated, although many excellent books on TRP channels have been published meanwhile, to jump into a new adventure editing a comprehensive source book in this successful Springer Handbook series again on the same topic. This is not only an update of the 2007 book but also an impressive introduction of novel areas which TRP channels have entered. The 2007 view that TRP channels are mainly cell sensors with an intriguing variability concerning the modes of activation has dramatically extended into the evolutionary field, the structural approach, and especially the advent of the important role of TRP channels in hereditary and acquired diseases. Important new data concerning the role of TRP channels in intracellular compartments are included. We also refer to the still controversial topic how TRP channel is involved in store-dependent Ca^{2+} entry. Indeed, the TRP field expansion did not lose the fast speed. It is extending into so far unexpected areas. The *gain of knowledge* has reached such an extent that we have not been able to restrict the source book into a single volume; rather, we had to agree on a two-volume publication. In the first volume, we go through all the known TRP channels. Leading experts in the field summarize features of individual TRP channels starting with the description of the gene, the expression patters, associated proteins, biophysical and biochemical function properties, and transgenic animal models and

[1] The used search string was ("transient receptor potential" OR trpa* OR trpc* OR trpm* OR trpp* OR trpv* OR PKD* OR stim1 OR stim2 OR orai1 OR orai2 OR orai3 OR trpa*). Note that this search included also the main players of store-operated Ca^{2+} entry, because of the still-often-reported links to TRP as also discussed in Volume 2.

closing with cellular TRP functions, dysfunctions, and their role in diseases. The second volume starts with a chapter on sensor properties and functions of TRP channels. This was highlighted in the 2007 book but is not very much extended. Surprising new features are reported, e.g., new insights into thermo- and light-sensing, novel roles or TRPs in taste perception and chemesthesis, and especially their functional importance as chemosensors for gasotransmitters, including oxygen sensing, which was evidenced only in the last 5 years. In the second part, more general topics related to TRP functions and features are discussed such as channel structure; TRPs as targets of pharmacological modulation, including a wealth of natural compounds; and the exciting discovery of novel channel toxins. New aspects are discussed concerning the role of TRPs as important players in the physiology of reproduction and in neural networks which control reproductive behavior opening a *TRP window* into neuroendocrinology, i.e., their role in hormone-secreting cells. We finish this book with some critical remarks on the current state of TRP research, controversies, and surprises.

We hope that this book will guide a large reader community through the fascinating world of the TRP channel family from basic science to pathophysiology and disease. May this voluminous source/textbook also help to establish interactions between the fundamental and clinical research and the research in drug discovery and development! We are convinced that this book is "translational" in the best meaning of this word. Despite the many advances in the understanding of the molecular mechanisms and function features of TRP channel, there is still a tremendous need for more in-depth understanding of the structure of TRP channels, their implementation in diverse signal cascades, more mechanistic insight into channel function at the molecular and systemic level, as well as the need for identifying selective pharmacological tools, new therapeutic targets, and developing new treatment options. We hope this book stimulates further research. Finally, we may conclude that we might be still in a period of the end of the beginning rather than the beginning of the end! The editors wish to thank all authors for excellent contribution and also Wilma McHugh (Springer) for all expert support and very helpful editorial advice!

Leuven Bernd Nilius
Homburg Veit Flockerzi

Contents for Volume I

TRPs: Truly Remarkable Proteins 1
Veit Flockerzi and Bernd Nilius

Part I The TRPC Subfamily

TRPC1 15
Vasyl Nesin and Leonidas Tsiokas

TRPC2 53
Barbara A. Miller

TRPC3: A Multifunctional Signaling Molecule 67
Michaela Lichtenegger and Klaus Groschner

TRPC4- and TRPC4-Containing Channels 85
Marc Freichel, Volodymyr Tsvilovskyy, and Juan E. Camacho-Londoño

TRPC5 129
Alexander V. Zholos

TRPC6: Physiological Function and Pathophysiological Relevance 157
Alexander Dietrich and Thomas Gudermann

Transient Receptor Potential Canonical 7: A Diacylglycerol-Activated Non-selective Cation Channel 189
Xuexin Zhang and Mohamed Trebak

Part II The TRPV Subfamily

TRPV1 207
Stuart Bevan, Talisia Quallo, and David A. Andersson

TRPV2 247
Itaru Kojima and Masahiro Nagasawa

TRPV3 273
Pu Yang and Michael X. Zhu

The TRPV4 Channel 293
Anna Garcia-Elias, Sanela Mrkonjić, Carole Jung, Carlos Pardo-Pastor, Rubén Vicente, and Miguel A. Valverde

TRPV5: A Ca^{2+} Channel for the Fine-Tuning of Ca^{2+} Reabsorption 321
Tao Na and Ji-Bin Peng

TRPV6 Channels 359
Claudia Fecher-Trost, Petra Weissgerber, and Ulrich Wissenbach

Part III The TRPM Subfamily

TRPM1 387
Shoichi Irie and Takahisa Furukawa

TRPM2 403
Malika Faouzi and Reinhold Penner

TRPM3 427
Johannes Oberwinkler and Stephan E. Philipp

TRPM4 461
Ilka Mathar, Griet Jacobs, Miklos Kecskes, Aurelie Menigoz, Koenraad Philippaert, and Rudi Vennekens

TRPM5 489
Emily R. Liman

TRPM6 503
Vladimir Chubanov and Thomas Gudermann

TRPM7 521
Andrea Fleig and Vladimir Chubanov

TRPM8 547
Laura Almaraz, Jan-Albert Manenschijn, Elvira de la Peña, and Félix Viana

Part IV The TRPA1, TRPML and TRPP Subfamilies

TRPA1 583
Peter M. Zygmunt and Edward D. Högestätt

TRPML1: An Ion Channel in the Lysosome 631
Wuyang Wang, Xiaoli Zhang, Qiong Gao, and Haoxing Xu

TRPML2 and Mucolipin Evolution 647
Jaime García-Añoveros and Teerawat Wiwatpanit

TRPML3 659
Christian Grimm, Maria Barthmes, and Christian Wahl-Schott

The TRPP Subfamily and Polycystin-1 Proteins 675
Mariam Semmo, Michael Köttgen, and Alexis Hofherr

Index 713

Contents for Volume II

Part V TRPs as Special Cell Sensors

TRP Channels and Thermosensation
Thomas Voets

TRPs in Mechanosensing and Volume Regulation
Tim D. Plant

TRPs as Chemosensors (ROS, RNS, RCS, Gasotransmitters)
Shunichi Shimizu, Nobuaki Takahashi, and Yasuo Mori

Photosensitive TRPs
Roger C. Hardie

TRPs in Taste and Chemesthesis
Stephen D. Roper

TRPs and Pain
Jane E. Sexton, Jeffrey Vernon, and John N. Wood

TRPs in Hearing
Damiano Zanini and Martin C. Göpfert

TRPs in Olfaction
Frank Zufall

Part VI General Topics

Evolutionarily Conserved, Multitasking TRP Channels: Lessons from Worms and Flies
Kartik Venkatachalam, Junjie Luo, and Craig Montell

Structural Biology of TRP Channels
Ute A. Hellmich and Rachelle Gaudet

High-Resolution Views of TRPV1 and Their Implications for the TRP Channel Superfamily
Ute A. Hellmich and Rachelle Gaudet

Physiological Functions and Regulation of TRPC Channels
Hwei Ling Ong, Lorena B. de Souza, Kwong Tai Cheng,
and Indu S. Ambudkar

The TRPCs–STIM1–Orai Interaction
Seok Choi, Jozsef Maleth, Archana Jha, Kyu Pil Lee, Min Seuk Kim,
Insuk So, Malini Ahuja, and Shmuel Muallem

The TRPC Family of TRP Channels: Roles Inferred (Mostly) from Knockout Mice and Relationship to ORAI Proteins
Yanhong Liao, Joel Abramowitz, and Lutz Birnbaumer

TRPs: Modulation by Drug-Like Compounds
Michael Schaefer

TRP Channels in Reproductive (Neuro)Endocrinology
Trese Leinders-Zufall and Ulrich Boehm

Modulation of TRP Ion Channels by Venomous Toxins
Jan Siemens and Christina Hanack

Phosphoinositide Regulation of TRP Channels
Tibor Rohacs

TRP Modulation by Natural Compounds
Flavia Carla Meotti, Edinéia Lemos de Andrade, and João B. Calixto

What Do We Really Know and What Do We Need to Know: Some Controversies, Perspectives, and Surprises
Bernd Nilius and Veit Flockerzi

Index

TRPs: Truly Remarkable Proteins

Veit Flockerzi and Bernd Nilius

Abstract

The family of transient receptor potential cation channels has received in the last 10 years a tremendous interest because members of this family are involved in a plethora of cell functions and have been identified as causal for many hereditary and acquired diseases. We shortly introduce these channels, summarize nomenclature and chromosomal location of the 28 mammalian *Trp* genes, and list the available *Trp*-deficient mouse lines.

Keywords

TRP cation channel proteins • TRP phylogenetic tree • *Trp* gene • Chromosomal location • *Trp* gene knockout • *Trp*-deficient mouse strain • Mouse (animal) model

The "transient receptor potential" (*trp*) gene was cloned from the Drosophila fly in 1989 (Montell and Rubin 1989), the molecular identification and functional characterization of the mammalian TRPC members occurred in 1995 (Wes et al. 1995; Zhu et al. 1995; Nilius and Owsianik 2011), and we are now, in 2014, probably just at the beginning to get a deeper understanding of the molecular structure, the biophysical properties, the functional role, and the pathophysiological impact of the 28 mammalian (27 human) members of this superfamily. The number of publications on this topic rises explosively ranging from molecular biology and crystallography to clinical research, food production, and cosmetics. So far, more

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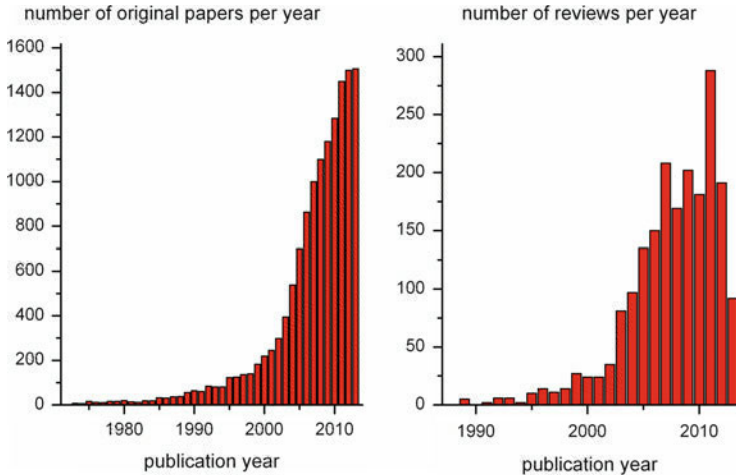

Fig. 1 Publications in the TRP field (adapted from PubMed, November 3, 2013)

than 13,000 publications and 2,000 reviews have been published about TRPs (Fig. 1). The increase in the last 20 years is nearly exponential! This flood of new information justifies hopefully a comprehensive source book which covers the state of the art in TRP research.

Transient receptor potential (TRP) cation channels have been extensively studied and described as polymodal cell sensors (Gees et al. 2010, 2012; Nilius and Owsianik 2011; Wu et al. 2010). They fall into six subfamilies (Fig. 2): TRPC for "canonical" (TRPC1–7), TRPV for "vanilloid" (TRPV1–6), TRPM for "melastatin" (TRPM1–8), TRPP for "polycystin" (TRPP2, TRPP3, TRPP5), TRPML for "mucolipin" (TRPML1–3), and TRPA for "ankyrin" (TRPA1). All TRP gene products are intrinsic membrane proteins with six putative transmembrane spans (S1–S6) and a cation-permeable pore region between S5 and S6. The length of the intracellular amino (N) and carboxy (C) termini and structural domains (e.g., ankyrin) they encompass varies significantly between members of the TRP channel subfamilies (Owsianik et al. 2006). The cytoplasmic domains are involved in the regulation and modulation of channel function and trafficking. Functional TRP channels consist of four identical or similar TRP subunits.

Table 1 summarizes the nomenclature used in this chapter and lists the chromosomal locations of the 28 *Trp* channel genes present in human and mouse. Whereas some chromosomes carry one up to three or four *Trp* genes (Table 2), only the *Trpv6* and *Trpv5* genes and the *Trpv1* and *Trpv3* genes are located side by side and in the same transcriptional orientation in single human and mouse chromosomes (Table 2) suggesting recent gene duplication events in the TRPV subfamily (Abramowitz and Birnbaumer 2007). In human *Trpv3* is located in chromosome 17 immediately before *Trpv1* (separated by 7.45 kbps). Similarly in mouse *Trpv3* is located in chromosome 11 immediately before *Trpv1* (separated by 6.15 kbps). The *Trpv6* gene is located in human chromosome 7 and mouse chromosome

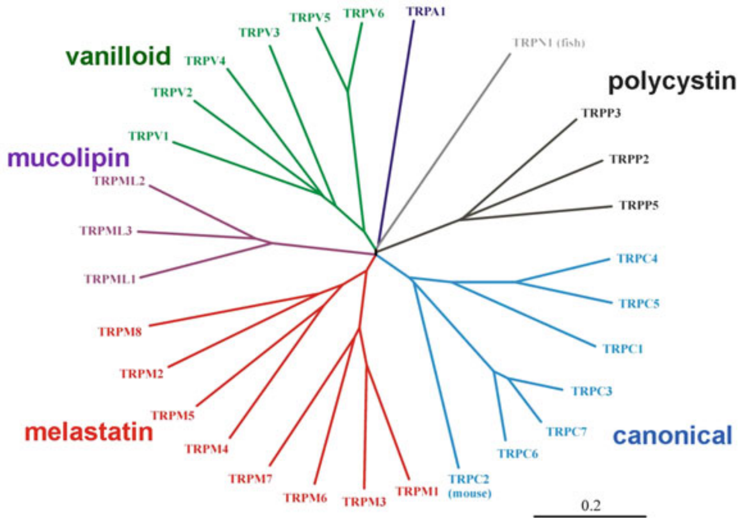

Fig. 2 The phylogenetic tree of the TRP family [adapted from Nilius and Owsianik (2011) with permission]

6, respectively, immediately in front of the *Trpv5* gene (separated by 21.76 kbps in human and by 16.37 kbps in mouse).

This handbook is published 7 years after the first TRP *Handbook of Experimental Pharmacology* (HEP) (Flockerzi and Nilius 2007) with the intention to focus our view on the most important achievements. We cover in detail all the 28 mammalian members of the TRP family, describing the gene, expression, channel functions, functional properties, interaction partners of TRP channels, diverse and complex signaling cascades, lessons from knockout models, and their impact on human diseases.

Especially TRP gene knockout animals, obtained by deletion of individual *Trp* genes in embryonic stem cells through homologous recombination, have made it possible to identify TRP channel functions and their relationship to physiological and pathophysiological processes in the living organism (Freichel et al. 2011). Since 2007 additional knockouts for 16 *Trp* genes have been published [compared to 10 before 2007 Freichel and Flockerzi (2007)], and at present only two *Trp* genes remain to be deleted, *Trpml2* and *Trpp5* (Table 3). Among the wealth of information obtained by phenotyping wild-type animals in comparison to the corresponding *Trp* gene-deficient animals (and described in the various chapters of this volume), two findings are striking: (1) With the exception of *Trpm7*-deficient (Jin et al. 2008), *Trpm6*-deficient (Walder et al. 2009), and *Trpp2*-deficient animals (Wu et al. 1998), all other knockouts are viable. *Trpm7*$^{-/-}$ embryos died before day 7.5 of embryogenesis, *Trpm6*$^{-/-}$ mice never survived to weaning and mostly died by embryonic day 12.5, and *Trpp2*$^{-/-}$ embryos died later than embryonic day 15. (2) Although several TRPs have been associated with fertility and reproduction,

Table 1 TRP nomenclature and chromosomal location of TRP channel genes in the human and mouse genomes

	Human			Mouse		
TRP	Gene	Chromosome	Location	Gene	Chromosome	Location
Trpa1	ENSG00000104321	8	72,932,152–72,987,852	ENSMUSG00000032769	1	14,872,648–14,918,862
Trpc1	ENSG00000144935	3	142,442,916-142,526,730	ENSMUSG00000032839	9	95,706,627-95,750,358
Trpc2	ENSG00000182048	11	3,631,131–3,658,789	ENSMUSG00000070425	7	102,065,511–102,096,864
Trpc3	ENSG00000138741	4	122,800,182–122,872,909	ENSMUSG00000027716	3	36,620,482–36,690,167
Trpc4	ENSG00000133107	13	38,210,773–38,444,562	ENSMUSG00000027748	3	54,156,057–54,318,470
Trpc5	ENSG00000072315	x	111,017,543–111,326,004	ENSMUSG00000041710	x	144,381,671–144,688,180
Trpc6	ENSG00000137672	11	101,322,295–101,743,293	ENSMUSG00000031997	9	8,544,196–8,680,565
Trpc7	ENSG00000069018	5	135,548,999–135,732,730	ENSMUSG00000021541	13	56,773,113–56,895,789
Trpm1	ENSG00000134160	15	31,293,264–31,453,476	ENSMUSG00000030523	7	64,153,835–64,269,775
Trpm2	ENSG00000142185	21	45,770,046–45,862,964	ENSMUSG00000009292	10	77,907,722–77,970,563
Trpm3	ENSG00000083067	9	73,149,949–74,061,820	ENSMUSG00000052387	19	22,139,119–22,989,884
Trpm4	ENSG00000130529	19	49,660,998–49,715,093	ENSMUSG00000038260	7	45,303,155–45,333,780
Trpm5	ENSG00000070985	11	2,425,745–2,444,275	ENSMUSG00000009246	7	143,069,153–143,094,642
Trpm6	ENSG00000119121	9	77,337,411–77,503,010	ENSMUSG00000024727	19	18,749,983–18,892,510
Trpm7	ENSG00000092439	15	50,844,670–50,979,012	ENSMUSG00000027365	2	126,791,565–126,876,230
Trpm8	ENSG00000144481	2	234,826,043–234,928,166	ENSMUSG00000036251	1	88,277,661–88,389,293
Trpv1	ENSG00000196689	17	3,468,738–3,500,392	ENSMUSG00000005952	11	73,234,292–73,261,242
Trpv2	ENSG00000187688	17	16,318,856–16,340,317	ENSMUSG00000018507	11	62,574,486–62,600,515
Trpv3	ENSG00000167723	17	3,413,796–3,461,289	ENSMUSG00000043029	11	73,267,388–73,300,363
Trpv4	ENSG00000111199	12	110,220,890–110,271,212	ENSMUSG00000014158	5	114,622,152–114,658,421
Trpv5	ENSG00000127412	7	142,605,267–142,630,905	ENSMUSG00000036899	6	41,652,770–41,680,723
Trpv6	ENSG00000165125	7	142,568,956–142,583,507	ENSMUSG00000029868	6	41,620,621–41,636,405
Trpml1	ENSG00000090674	19	7,587,512–7,598,895	ENSMUSG00000004567	8	3,500,457–3,515,232
Trpml2	ENSG00000153898	1	85,391,268–85,462,796	ENSMUSG00000011008	3	146,149,833–146,195,513

Trpml3	ENSG00000055732	1	85,483,765–85,514,182	ENSMUSG00000036853	3	146,117,459–146,141,806
Trpp2	ENSG00000118762	4	88,928,820–88,998,929	ENSMUSG00000034462	5	104,459,450–104,505,819
Trpp3	ENSG00000107593	10	102,047,903–102,090,243	ENSMUSG00000037578	19	44,147,637–44,192,442
Trpp5	ENSG00000078795	5	137,223,657–137,278,436	ENSMUSG00000014503	18	34,409,423–34,442,789

Gene resource: http://www.ensembl.org

Table 2 Know thy neighbor: chromosomal location of human and mouse *Trp* genes

Chromosome	Homo sapiens	Mus musculus
1	*Trpml2*+ *Trpml3*−	*Trpa1*− *Trpm8*+
2	*Trpm8*+	*Trpm7*−
3	*Trpc1*+	*Trpc3*− *Trpc4*+ *Trpml3*+ *Trpml2*+
4	*Trpp2*+ *Trpc3*−	
5	*Trpp5*+ *Trpc7*−	*Trpp2*+ *Trpv4*−
6		*Trpv6*−/*Trpv5*−
7	*Trpv6*−/*Trpv5*−	*Trpm4*− *Trpm1*+ *Trpc2*+ *Trpm5*−
8	*Trpa1*−	*Trpml1*+
9	*Trpm3*− *Trpm6*−	*Trpc6*+ *Trpc1*−
10	*Trpp3*−	*Trpm2*−
11	*Trpm5*− *Trpc2*+	*Trpv2*+ *Trpv1*+/*Trpv3*+
12	*Trpc6*− *Trpv4*−	
13	*Trpc4*−	*Trpc7*−
14		
15	*Trpm1*− *Trpm7*−	
16		
17	*Trpv3*−/*Trpv1*− *Trpv2*+	
18		*Trpp5*+
19	*Trpml1*+ *Trpm4*+	*Trpm6*+ *Trpm3*+ *Trpp3*−
20		
21	*Trpm2*+	
22		
x	*Trpc5*−	*Trpc5*−
y		

Back to back are *Trpv6*/*Trpv5* (human, chromosome 7, and mouse, chromosome 6) and *Trpv3*/*Trpv1* (human, chromosome 17, and mouse, chromosome 11); +, forward strand; −, reverse strand

only TRPV6 channels have been shown to be essential for (mouse male) fertility (Weissgerber et al. 2011, 2012).

So far half of the published knockouts are conventional or global knockouts (Table 3). The gene deletion is unrestricted and animals inherit the genetic deletion in all of their cell types. In these animals, it may be difficult to exclude the possibility that developmental defects or compensatory upregulation of other genes contributes to the phenotype observed in adult animals. In addition, this global gene deletion might make it difficult to attribute abnormal phenotypes to a particular type of cell. The other half are conditional knockouts (Table 3) which allow regional and temporal control of TRP gene expression and that restrict deletions to cells in a specific tissue or at specific points in an animal's development. More of these conditional TRP-deficient mouse models are required.

Other strategies allow visualizing TRP-expressing cells. These strategies include generation of TRP-dependent reporter-tagged null mutations as shown for TRPA1 [*alkaline phosphatase* (Kwan et al. 2006)], TRPM8 [*eGFP* (Dhaka et al. 2007) or *lacZ* (Colburn et al. 2007)], and TRPM3 [*lacZ* (Vriens et al. 2011)]. Whereas the

Table 3 *Trp*-deficient mice

Gene	Deletion of exon(s)	Conditional	References
Trpa1	23 (part.)	No	Bautista et al. (2006)
	22–24, replaced by *IRES-alkaline phosphatase-polyA*-cassette	No	Kwan et al. (2006)
Trpc1	8	No	Dietrich et al. (2007)
Trpc2	7–10	No	Stowers et al. (2002)
	6–11	No	Leypold et al. (2002)
Trpc3	7	Yes	Hartmann et al. (2008)
	7–8	Yes	Hirschler-Laszkiewicz et al. (2012)
Trpc4	6	No	Freichel et al. (2001)
Trpc5	5	Yes	Riccio et al. (2009)
	4	Yes	Xue et al. (2011)
Trpc6	7	No	Dietrich et al. (2005)
Trpc7	1	Yes	Perez-Leighton et al. (2011)
	5	Yes	Xue et al. (2011)
Trpv1	9, 10, 11 (part.)	No	Caterina et al. (2000)
Trpv2	10–13	Yes	Park et al. (2011)
Trpv3	14–15	No	Moqrich et al. (2005)
Trpv4	4	No	Suzuki et al. (2003)
	12	Yes	Liedtke and Friedman (2003)
Trpv5	13	Yes	Hoenderop et al. (2003)
Trpv6	9–15	No	Bianco et al. (2007)
	13–15	Yes	Weissgerber et al. (2012)
Trpm1	2–4	No	Morgans et al. (2009)
	3 (part.)–5	No	Shen et al. (2009)
	4–6	No	Koike et al. (2010)
Trpm2	20–21	No	Yamamoto et al. (2008)
Trpm3	19 (part.) replaced by *IRES- lacZ-neo*-cassette	No	Vriens et al. (2011)
Trpm4	15–16	Yes	Vennekens et al. (2007)
	3–6	Yes	Barbet et al. (2008)
Trpm5	15–19	No	Zhang et al. (2003)
	Promoter, 1–4	No	Damak et al. (2006)
Trpm6	5–7	No	Walder et al. (2009)
	2–3 replaced by *IRES- lacZ-neo*-cassette	No	Woudenberg-Vrenken et al. (2011)
Trpm7	Intron 1 (insertion)	No	Jin et al. (2008)
	17	Yes	Jin et al. (2008)
	32–36 (kinase)	No	Ryazanova et al. (2010)
Trpm8	1–2, replaced by *lacZ-neo*-cassette	No	Colburn et al. (2007)
	Knock-in of *eGFP-polyA*-cassette into exon 5, 27 nt following start	No	Dhaka et al. (2007)
	13–14	No	Bautista et al. (2007)

(continued)

Table 3 (continued)

Gene	Deletion of exon(s)	Conditional	References
Trpp2	1 (insertion)	No	Wu et al. (1998)
	1	No	Pennekamp et al. (2002)
Trpp3	3–9	No	Horio et al. (2011)
Trpp5	n.d.		
Trpml1	3–5 (part.)	Yes	Venugopal et al. (2007)
Trpml2	n.d.		
Trpml3	11	Yes	Jors et al. (2010)
	7–8	Yes	Castiglioni et al. (2011)

Part. partial, *n.d.* not described, *nt* nucleotides; *conditional, no,* refers to conventional or global gene deficiency

TRPA1 and TRPM8 mice have been generated by gene targeting approaches, the TRPM3 mouse and one of the TRPM6 mouse strains were generated by gene trapping. The visualization of TRP-expressing cells could also be accomplished by mouse lines, which carry an internal ribosome entry site (IRES) followed by the cDNA of a Cre recombinase within the *Trp* gene. In this strategy the IRES element will result in transcription of a bicistronic messenger RNA from which the TRP and cre recombinase are independently translated. These TRP-IRES-Cre animals can be bred to reporter mice where the “reporter,” the cDNA of a marker gene (e.g., *LacZ*, *GFP*, *CFP*, or *YFP*), is expressed only following Cre-mediated recombination (Fig. 3). So far, no such TRP-IRES-Cre mouse lines obtained by homologous recombination have been published, but several are in various pipelines. By these strategies, TRP-positive cells can be directly visualized and additionally manipulated in various ways depending on the properties of the “reporter” genes (channelrhodopsin, diphtheria toxin, calcium indicators, etc.) used.

In this volume, the special progress of studying TRP channels in intracellular organelles, such as TRPML channels in endosomes and lysosomes, will also be highlighted. In addition, we provide in detail an overview on special cellular functions of these channels such as photoreception, hearing, olfaction, taste, and somatosensation such as nociception, mechanoreception, temperature sensing, chemosensing, i.e., all the classical Aristotle’s senses which are so much depending on TRPs. TRPs were first considered as unique cell sensors which are involved in all our Aristotle’s senses by which we discover the world (Damann et al. 2008). However, TRP channels have a much higher functional importance than just acting as sensory channels. They play an important role in many homeostatic functions. These aspects will also be discussed in this book. In addition, some exciting new developments, e.g., the modulation of TRPs by a plethora of natural compounds, the role of TRPs in endocrinology and metabolic control, the exciting interaction with STIM, ORAI, components of the molecular machinery which constitutes store-operated Ca^{2+} entry.

From the point of view of fundamental research, TRPs show a unique promiscuity of gating mechanisms which came as a surprise even for channel maniacs [for

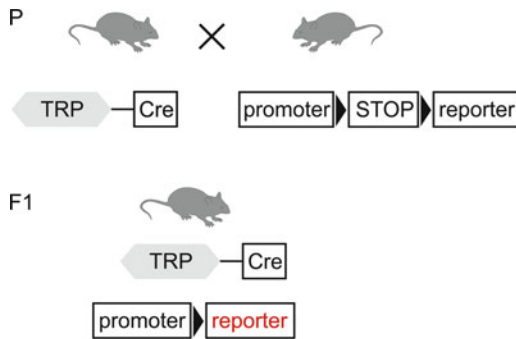

Fig. 3 Strategy to visualize and manipulate TRP-expressing cells. Mice carrying a targeted integration of the cDNA of cre recombinase (Cre) within a *Trp* gene (TRP) are mated with mice carrying a (floxed) strong transcriptional termination sequence (STOP) followed by the cDNA of the "reporter" under the control of a (constitutively and ubiquitously expressed) promoter (reporter strain). P, parental mice. After Cre-mediated recombination, the floxed "STOP" cDNA is excised allowing the promoter to drive expression of the reporter. Black triangles represent loxP target sites for Cre-mediated recombination. A multitude of strains have been created using the cDNAs of fluorescent proteins (channelrhodopsin2, lacZ, diphtheria toxin A, halorhodopsin, and reverse tetracycline transactivator, to name only a few) by targeted insertion of a reporter gene in the ubiquitously expressed Rosa26 locus (Soriano 1999)

a comprehensive review, see Gees et al. (2012)]. TRPs are probably expressed in all cells of our body. It was therefore not unexpected that TRP channels are involved in several, still not well-understood diseases and have therefore triggered a huge hope for the development of new drug targeting these channels (Moran et al. 2011; Nilius et al. 2007; Nilius and Voets 2013).

We hope that this book will provide the most actual overview on the different faces of these channels written by world leaders in this field. Another—maybe more sophisticated—answer is that we know a lot about TRPs but we understand a lot less about the 28 mammalian members of this channel superfamily than of other ion channels. It is therefore important to reevaluate and reinterpret even the well-known data under the view of all new achievements. Hopefully this book issue will serve this important task to describe in a really up-to-date fashion these *truly remarkable* TRP *proteins*!

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Part I

The TRPC Subfamily

TRPC1

Vasyl Nesin and Leonidas Tsiokas

Contents

1 Introduction 16
2 Gene Structure 18
3 Expression 19
4 Channel Protein Including Structural Aspects 20
  4.1 Pore-Forming Domain 20
  4.2 N- and C-Terminal Cytosolic Fragments 20
  4.3 N-Terminal Extension 21
5 Interacting Proteins 21
  5.1 Channel Subunits 21
  5.2 Cell Surface Receptors 23
  5.3 Cytosolic Proteins 25
6 Channel Function, Permeation, and Gating 28
  6.1 Activation by Store Depletion 28
  6.2 Activation by Receptor Stimulation 30
  6.3 Activation by Mechanical Forces 32
  6.4 Permeation-Single Channel Conductance 32
7 Physiological Functions in Native Cells, Organs, and Organ Systems 33
  7.1 Cardiovascular System 33
  7.2 Skeletal Muscle 34
  7.3 Neurons 35
  7.4 Salivary Gland Cells 35
  7.5 Bone 36
8 Lessons from Knockout Mice 37
9 Role in Hereditary and Acquired Diseases 39
  9.1 Diabetic Nephropathy 39
  9.2 Parkinson's Disease 40
  9.3 Huntington's Disease 40

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9.4 Cancer ... 40
9.5 Duchenne Muscular Dystrophy ... 40
9.6 Seizures and Epilepsy ... 41
9.7 Darier–White Disease ... 41
References ... 41

Abstract

The TRPC1 ion channel was the first mammalian TRP channel to be cloned. In humans, it is encoded by the *TRPC1* gene located in chromosome 3. The protein is predicted to consist of six transmembrane segments with the N- and C-termini located in the cytoplasm. The extracellular loop connecting transmembrane segments 5 and 6 participates in the formation of the ionic pore region. Inside the cell, TRPC1 is present in the endoplasmic reticulum, plasma membrane, intracellular vesicles, and primary cilium, an antenna-like sensory organelle functioning as a signaling platform. In human and rodent tissues, it shows an almost ubiquitous expression. TRPC1 interacts with a diverse group of proteins including ion channel subunits, receptors, and cytosolic proteins to mediate its effect on Ca^{2+} signaling. It primarily functions as a cation nonselective channel within pathways controlling Ca^{2+} entry in response to cell surface receptor activation. Through these pathways, it affects basic cell functions, such as proliferation and survival, differentiation, secretion, and cell migration, as well as cell type-specific functions such as chemotropic turning of neuronal growth cones and myoblast fusion. The biological role of TRPC1 has been studied in genetically engineered mice where the *Trpc1* gene has been experimentally ablated. Although these mice live to adulthood, they show defects in several organs and tissues, such as the cardiovascular, central nervous, skeletal and muscular, and immune systems. Genetic and functional studies have implicated TRPC1 in diabetic nephropathy, Parkinson's disease, Huntington's disease, Duchenne muscular dystrophy, cancer, seizures, and Darier–White skin disease.

Keywords

Channel • TRP • Calcium signaling • Disease

1 Introduction

G-protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs) comprise a very large group of cell surface receptors that elicit their physiological responses through the production of inositol-1,4,5-trisphosphate (IP_3) (Berridge and Irvine 1984) (Fig. 1). Receptor stimulation results in the activation of PLC-β or γ isoforms, which catalyze the formation of IP_3 and diacylglycerol (DAG) from phosphatidylinositol-4,5-bisphosphate (PIP_2). Newly synthesized IP_3 acts on IP_3 receptors (IP_3Rs) to trigger a rapid increase in the intracellular Ca^{2+} concentration

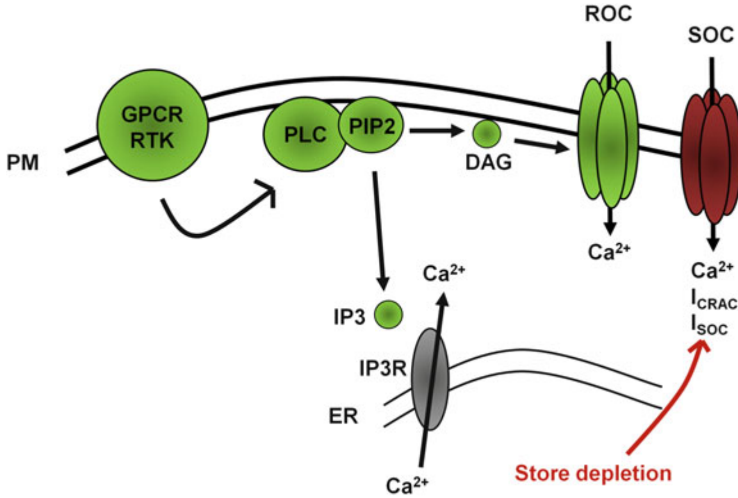

Fig. 1 Diagram illustrating activation mechanisms of receptor- and store-operated Ca^{2+} entry channels. Agonist stimulation of a G-protein-coupled receptor (GPCR) or receptor tyrosine kinase (RTK) in the plasma membrane (PM) results in the activation of phospholipase C-β or γ, respectively, and production of diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3) from phosphatidylinositol-4,5-bisphosphate (PIP_2). IP_3 induces a rapid Ca^{2+} release from the endoplasmic reticulum (ER) by acting through the IP_3 receptors (IP3Rs) on the ER. Ca^{2+} release causes a rapid depletion of Ca^{2+} in the ER resulting in the activation of store-operated Ca^{2+} (SOC) entry channels (shown in *burgundy*) in the PM. SOCs can mediate the highly Ca^{2+}-selective, Ca^{2+}-release-activated Ca^{2+} current (I_{CRAC}) or the less Ca^{2+}-selective, store-operated channel current (I_{SOC}). Receptor-operated channels (ROC, shown in *green*) are activated by second messengers generated in response to the activation of a given GPCR or RTK, but not by store depletion

by releasing free Ca^{2+} from intracellular stores (Burgess et al. 1984). Intracellular Ca^{2+} concentration returns to normal levels by extrusion of cytoplasmic Ca^{2+} to the extracellular space mediated by plasma membrane Ca^{2+}-ATPases and Na^{+}–Ca^{2+} exchangers, readmission of Ca^{2+} into the endoplasmic reticulum (ER) mediated by the SERCA pump, and Ca^{2+} entry via the store- and receptor- operated Ca^{2+} channels (Fasolato et al. 1994; Putney and McKay 1999). Store- and receptor-operated Ca^{2+} entry maintains Ca^{2+} homeostasis and keeps the cell in a Ca^{2+} signaling-competent stage. Both processes are needed for diverse cellular functions (Parekh and Penner 1997) ranging from cell proliferation and gene expression in T lymphocytes (Lewis 2001) to endothelial cell function (Nilius and Droogmans 2001) and regulation of the acrosome reaction in germ cells (Wassarman et al. 2001).

In general, store-operated channels are the channels defined by their ability to open in response to the depletion of the internal Ca^{2+} stores, but the term receptor-operated channels is loosely defined (also discussed in (Patterson et al. 2002)). According to one of the two widely used definitions, receptor-operated channels are the channels activated in response to the activation of an IP_3-coupled receptor. Therefore, the term is inclusive of both store-operated and second messenger-

activated channels (Barritt 1999). The other usage of the term is applied to describe channels activated directly by second messengers (i.e., DAG or cell-permeant derivatives such as 1-oleoyl-2-acetyl-sn-glycerol, OAG) and not by store depletion, following receptor stimulation (Patterson et al. 2002). To avoid confusion, here we will adopt the latter definition (Fig. 1). Therefore, cell surface receptor stimulation will result in the activation of both store- and receptor-operated channels, whereas depletion of internal stores will result in the activation of only the store-operated channels (Fig. 1).

Store-operated Ca^{2+} entry channels can be divided into several types based on their biophysical properties (Parekh and Putney 2005). The prototypical Ca^{2+}-release-activated Ca^{2+} current (I_{CRAC}) was first described in mast cells (Hoth and Penner 1992), and its biophysical and pharmacological properties have been characterized in great detail (Hoth and Penner 1992; Zweifach and Lewis 1995). It is mediated by the CRAC channel which consists of the pore-forming subunits Orai1–3 (or CRAC modulator 1–3) and requires the Ca^{2+} sensors, STIM1 and STIM2, for activation (Hogan et al. 2010; Soboloff et al. 2012; Vig and Kinet 2009). In addition to I_{CRAC}, there are other store depletion-activated currents whose properties deviate to various degrees from the ones ascribed to I_{CRAC}. These currents are mediated by channels that show lower selectivity to Ca^{2+} compared to CRAC channel and called store-operated channels (SOCs) (Birnbaumer 2009; Lee et al. 2010; Parekh and Putney 2005; Worley et al. 2007). TRPC1 has been shown to modulate I_{CRAC} (Mori et al. 2002; Ong et al. 2013) and I_{SOC} (Cheng et al. 2008, 2011a; Huang et al. 2006; Liao et al. 2007, 2008; Shi et al. 2012; Singh et al. 2002; Yuan et al. 2003, 2007; Kiselyov et al. 1998; Zhu et al. 1996).

Receptor-operated channels (ROCs) fall into a group of ion channels activated by diverse stimuli generated in response to the activation of a cell surface receptor (Fig. 1). Second messengers that are generated in response to the activation of a receptor coupled to the phosphoinositide pathway can activate ion channels independently of store depletion. These messengers can include are DAG, PIP_2 hydrolysis, protein kinase C activation, increase in intracellular Ca^{2+} concentration following Ca^{2+} release from the ER, products of certain types of phospholipases, etc. (Fig. 1). A subgroup of the TRPC subfamily, such as TRPC3/6/7, is considered typical receptor-operated channels since they are activated by DAG/OAG (Hofmann et al. 1999). As it will be discussed later, TRPC1 has been shown to modulate Ca^{2+} influx mediated by the CRAC, SOC, and ROC channels.

2 Gene Structure

The primary amino acid sequence of TRPC1 was deduced almost 20 years ago (Zhu et al. 1995; Wes et al. 1995). The *TRPC1* gene is located in human chromosome 3q23. It consists of 13 distinct introns bearing GT-AG borders and 13 exons and spans a total of 83.84 kb of genomic sequence, from 142442902 to 142526737 (NCBI 37, August 2010), on the direct strand. Exon 1 contains the translation initiation start site. The *Trpc1* gene generates at least five reported splice variants in