

Bernd Nilius
Veit Flockerzi *Editors*

Mammalian Transient Receptor Potential (TRP) Cation Channels

Volume I

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Volume 222

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Editors

Mammalian Transient Receptor Potential (TRP) Cation Channels

Volume I

 Springer

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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 Ca²⁺ 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 patterns, 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 Ca²⁺ 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 of 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
Homburg

Bernd Nilius
Veit Flockerzi

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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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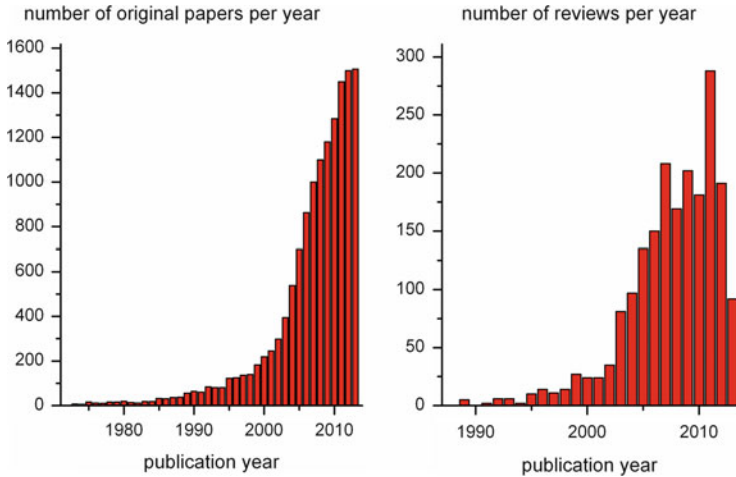


Fig. 1 Publications in the TRP field (adapted from PubMed, November 3, 2013)

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

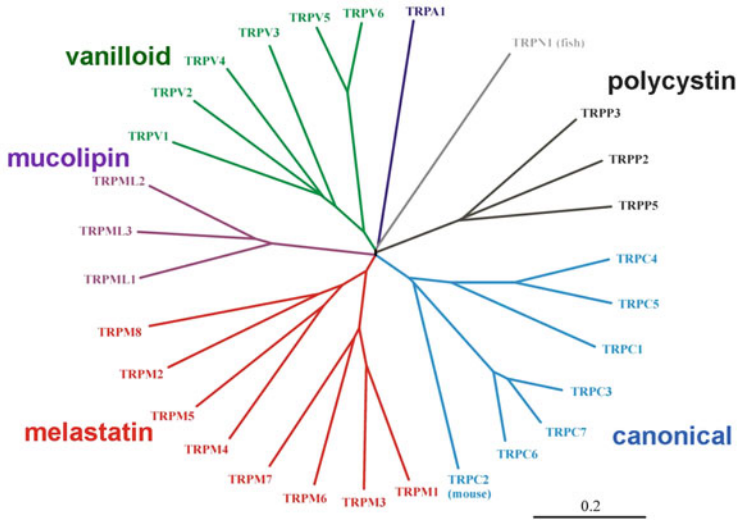


Fig. 2 The phylogenetic tree of the TRP family [adapted from Nilius and Owsianik (2011) with permission]

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

TRP	Human			Mouse		
	Gene	Chromosome	Location	Gene	Chromosome	Location
<i>Trpa1</i>	ENSG00000104321	8	72,932,152–72,987,852	ENSMUSG00000032769	1	14,872,648–14,918,862
<i>Trpc1</i>	ENSG00000144935	3	142,442,916–142,526,730	ENSMUSG00000032839	9	95,706,627–95,750,358
<i>Trpc2</i>	ENSG00000182048	11	3,631,131–3,658,789	ENSMUSG00000070425	7	102,065,511–102,096,864
<i>Trpc3</i>	ENSG00000138741	4	122,800,182–122,872,909	ENSMUSG00000027716	3	36,620,482–36,690,167
<i>Trpc4</i>	ENSG00000133107	13	38,210,773–38,444,562	ENSMUSG00000027748	3	54,156,057–54,318,470
<i>Trpc5</i>	ENSG00000072315	x	111,017,543–111,326,004	ENSMUSG000000041710	x	144,381,671–144,688,180
<i>Trpc6</i>	ENSG00000137672	11	101,322,295–101,743,293	ENSMUSG000000031997	9	8,544,196–8,680,565
<i>Trpc7</i>	ENSG00000069018	5	135,548,999–135,732,730	ENSMUSG00000021541	13	56,773,113–56,895,789
<i>Trpm1</i>	ENSG00000134160	15	31,293,264–31,453,476	ENSMUSG00000030523	7	64,153,835–64,269,775
<i>Trpm2</i>	ENSG00000142185	21	45,770,046–45,862,964	ENSMUSG00000009292	10	77,907,722–77,970,563
<i>Trpm3</i>	ENSG00000083067	9	73,149,949–74,061,820	ENSMUSG00000052387	19	22,139,119–22,989,884
<i>Trpm4</i>	ENSG00000130529	19	49,660,998–49,715,093	ENSMUSG00000038260	7	45,303,155–45,333,780
<i>Trpm5</i>	ENSG00000070985	11	2,425,745–2,444,275	ENSMUSG00000009246	7	143,069,153–143,094,642
<i>Trpm6</i>	ENSG00000119121	9	77,337,411–77,503,010	ENSMUSG00000024727	19	18,749,983–18,892,510
<i>Trpm7</i>	ENSG00000092439	15	50,844,670–50,979,012	ENSMUSG00000027365	2	126,791,565–126,876,230
<i>Trpm8</i>	ENSG00000144481	2	234,826,043–234,928,166	ENSMUSG00000036251	1	88,277,661–88,389,293
<i>Trpv1</i>	ENSG00000196689	17	3,468,738–3,500,392	ENSMUSG00000005952	11	73,234,292–73,261,242
<i>Trpv2</i>	ENSG00000187688	17	16,318,856–16,340,317	ENSMUSG00000018507	11	62,574,486–62,600,515
<i>Trpv3</i>	ENSG00000167723	17	3,413,796–3,461,289	ENSMUSG00000043029	11	73,267,388–73,300,363
<i>Trpv4</i>	ENSG00000111199	12	110,220,890–110,271,212	ENSMUSG00000014158	5	114,622,152–114,658,421
<i>Trpv5</i>	ENSG00000127412	7	142,605,267–142,630,905	ENSMUSG00000036899	6	41,652,770–41,680,723
<i>Trpv6</i>	ENSG00000165125	7	142,568,956–142,583,507	ENSMUSG00000029868	6	41,620,621–41,636,405
<i>Trpm1l</i>	ENSG00000090674	19	7,587,512–7,598,895	ENSMUSG00000004567	8	3,500,457–3,515,232
<i>Trpm2l</i>	ENSG00000153898	1	85,391,268–85,462,796	ENSMUSG00000011008	3	146,149,833–146,195,513

<i>Trpm13</i>	ENSG00000055732	1	85,483,765–85,514,182	ENSMUSG00000036853	3	146,117,459–146,141,806
<i>Trpp2</i>	ENSG00000118762	4	88,928,820–88,998,929	ENSMUSG00000034462	5	104,459,450–104,505,819
<i>Trpp3</i>	ENSG00000107593	10	102,047,903–102,090,243	ENSMUSG00000037578	19	44,147,637–44,192,442
<i>Trpp5</i>	ENSG00000078795	5	137,223,657–137,278,436	ENSMUSG000000014503	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	<i>Trpml2+</i> <i>Trpml3-</i>	<i>Trpa1-</i> <i>Trpm8+</i>
2	<i>Trpm8+</i>	<i>Trpm7-</i>
3	<i>Trpc1+</i>	<i>Trpc3-</i> <i>Trpc4+</i> <i>Trpml3+</i> <i>Trpml2+</i>
4	<i>Trpp2+</i> <i>Trpc3-</i>	
5	<i>Trpp5+</i> <i>Trpc7-</i>	<i>Trpp2+</i> <i>Trpv4-</i>
6		<i>Trpv6-/Trpv5-</i>
7	<i>Trpv6-/Trpv5-</i>	<i>Trpm4-</i> <i>Trpm1+</i> <i>Trpc2+</i> <i>Trpm5-</i>
8	<i>Trpa1-</i>	<i>Trpml1+</i>
9	<i>Trpm3-</i> <i>Trpm6-</i>	<i>Trpc6+</i> <i>Trpc1-</i>
10	<i>Trpp3-</i>	<i>Trpm2-</i>
11	<i>Trpm5-</i> <i>Trpc2+</i>	<i>Trpv2+</i> <i>Trpv1+/Trpv3+</i>
12	<i>Trpc6-</i> <i>Trpv4-</i>	
13	<i>Trpc4-</i>	<i>Trpc7-</i>
14		
15	<i>Trpml-</i> <i>Trpm7-</i>	
16		
17	<i>Trpv3-/Trpv1-</i> <i>Trpv2+</i>	
18		<i>Trpp5+</i>
19	<i>Trpml1+</i> <i>Trpm4+</i>	<i>Trpm6+</i> <i>Trpm3+</i> <i>Trpp3-</i>
20		
21	<i>Trpm2+</i>	
22		
x	<i>Trpc5-</i>	<i>Trpc5-</i>
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
<i>Trpal</i>	23 (part.)	No	Bautista et al. (2006)
	22–24, replaced by <i>IRES-alkaline phosphatase-polyA-cassette</i>	No	Kwan et al. (2006)
<i>Trpc1</i>	8	No	Dietrich et al. (2007)
<i>Trpc2</i>	7–10	No	Stowers et al. (2002)
	6–11	No	Leypold et al. (2002)
<i>Trpc3</i>	7	Yes	Hartmann et al. (2008)
	7–8	Yes	Hirschler-Laszkiewicz et al. (2012)
<i>Trpc4</i>	6	No	Freichel et al. (2001)
<i>Trpc5</i>	5	Yes	Riccio et al. (2009)
	4	Yes	Xue et al. (2011)
<i>Trpc6</i>	7	No	Dietrich et al. (2005)
<i>Trpc7</i>	1	Yes	Perez-Leighton et al. (2011)
	5	Yes	Xue et al. (2011)
<i>Trpv1</i>	9, 10, 11 (part.)	No	Caterina et al. (2000)
<i>Trpv2</i>	10–13	Yes	Park et al. (2011)
<i>Trpv3</i>	14–15	No	Moqrich et al. (2005)
<i>Trpv4</i>	4	No	Suzuki et al. (2003)
	12	Yes	Liedtke and Friedman (2003)
<i>Trpv5</i>	13	Yes	Hoenderop et al. (2003)
<i>Trpv6</i>	9–15	No	Bianco et al. (2007)
	13–15	Yes	Weissgerber et al. (2012)
<i>Trpm1</i>	2–4	No	Morgans et al. (2009)
	3 (part.)–5	No	Shen et al. (2009)
	4–6	No	Koike et al. (2010)
<i>Trpm2</i>	20–21	No	Yamamoto et al. (2008)
<i>Trpm3</i>	19 (part.) replaced by <i>IRES-lacZ-neo-cassette</i>	No	Vriens et al. (2011)
<i>Trpm4</i>	15–16	Yes	Vennekens et al. (2007)
	3–6	Yes	Barbet et al. (2008)
<i>Trpm5</i>	15–19	No	Zhang et al. (2003)
	Promoter, 1–4	No	Damak et al. (2006)
<i>Trpm6</i>	5–7	No	Walder et al. (2009)
	2–3 replaced by <i>IRES-lacZ-neo-cassette</i>	No	Woudenberg-Vrenken et al. (2011)
<i>Trpm7</i>	Intron 1 (insertion)	No	Jin et al. (2008)
	17	Yes	Jin et al. (2008)
	32–36 (kinase)	No	Ryazanova et al. (2010)
<i>Trpm8</i>	1–2, replaced by <i>lacZ-neo-cassette</i>	No	Colburn et al. (2007)
	Knock-in of <i>eGFP-polyA-cassette</i> 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
<i>Trpp2</i>	1 (insertion)	No	Wu et al. (1998)
	1	No	Pennekamp et al. (2002)
<i>Trpp3</i>	3–9	No	Horio et al. (2011)
<i>Trpp5</i>	n.d.		
<i>Trpml1</i>	3–5 (part.)	Yes	Venugopal et al. (2007)
<i>Trpml2</i>	n.d.		
<i>Trpml3</i>	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

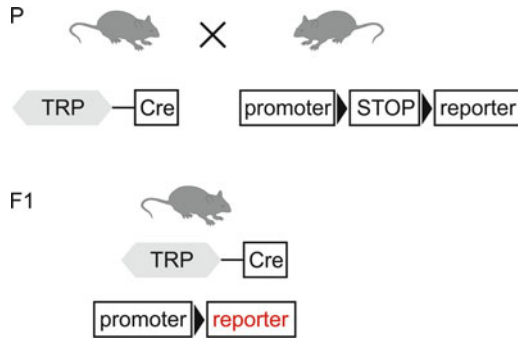


Fig. 3 Strategy to visualize and manipulate TRP-expressing cells. Mice carrying a targeted integration of the cDNA of cre recombinase (Cre) within a *Trp* gene (TRP) are mated with mice carrying a (floxed) strong transcriptional termination sequence (STOP) followed by the cDNA of the “reporter” under 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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