The role of TRP proteins in mast cells

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Transient receptor potential (TRP) proteins form cation channels that are regulated through strikingly diverse mechanisms including multiple cell surface receptors, changes in temperature, in pH and osmolarity, in cytosolic free Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_i\)), and by phosphoinositides which makes them polymodal sensors for fine tuning of many cellular and systemic processes in the body. The 28 TRP proteins identified in mammals are classified into six subfamilies: TRPC, TRPV, TRPM, TRPA, TRPML, and TRPP. When activated, they contribute to cell depolarization and Ca\(^{2+}\) entry. In mast cells, the increase of [Ca\(^{2+}\)]\(_i\) is fundamental for their biological activity, and several entry pathways for Ca\(^{2+}\) and other cations were described including Ca\(^{2+}\) release activated Ca\(^{2+}\) (CRAC) channels. Like in other non-excitatory cells, TRP channels could directly contribute to Ca\(^{2+}\) influx via the plasma membrane as constituents of Ca\(^{2+}\) conducting channel complexes or indirectly by shifting the membrane potential and regulation of the driving force for Ca\(^{2+}\) entry through independent Ca\(^{2+}\) entry channels. Here, we summarize the current knowledge about the expression of individual Trp genes with the majority of the 28 members being yet identified in different mast cell models, and we highlight mechanisms how they can regulate mast cell functions. Since specific agonists or blockers are still lacking for most members of the TRP family, studies to unravel their function and activation mode still rely on experiments using genetic approaches and transgenic animals. RNAi approaches suggest a functional role for TRPC1, TRPC5, and TRPM7 in mast cell derived cell lines or primary mast cells, and studies using Trp gene knock-out mice reveal a critical role for TRPM4 in mast cell activation and for mast cell mediated cutaneous anaphylaxis, whereas a direct role of cold- and menthol-activated TRPM8 channels seems to be unlikely for the development of cold urticaria at least in mice.

Keywords: TRP proteins, cation channels, Ca\(^{2+}\) signaling, mast cell activation
Also, replacement of external Ca\(^{2+}\) phosphatidylinositol (4,5) bisphosphate (PIP\(_2\)) to diacylglycerol (DAG) and inositol (1,4,5) trisphosphate (IP\(_3\)) following activation with other Ca\(^{2+}\) is described later also in mast cells (Putney, 1986; Ali et al., 1994; Gross et al., 2007). SOCE is substantially shown to be expressed in RBL-2H3 cells and bone marrow-derived mast cells (Gwack et al., 2008), and another protein called stromal interaction molecule 1 (Stim1) was shown to represent the Ca\(^{2+}\) entry pathway in primary murine and human mast cells (Turner et al., 2007), and TRPV5, appeared not to match the pore properties of CRAC channels (see below and Owssianik et al., 2006b).

Recently, Orai1 (also known as CRACM1) was identified as the pore-forming CRAC channel subunit (Feske et al., 2006; Vig et al., 2006; Lewis, 2007) and another protein called stomal interaction molecule 1 (Stim1) was shown to represent the Ca\(^{2+}\) sensor (Zweifach and Lewis, 1996). However, the pore properties of most TRP channels have been studied in detail, including TRPV6, which was identified in primary murine and human mast cells (Turner et al., 2007), and TRPV5, which is the receptor for vanilloids such as capsaicin, or by positional cloning efforts to identify genes disrupted in human diseases, e.g., polycystin-1, PC1 (also known as polycystin-2, PKD2, PC2) in autosomal polycystic kidney disease.

TRP PROTEINS FORM CATION CHANNELS

Transient receptor potential channels are a large and functionally heterogeneous family of cation-conducting channel proteins, which are activated and regulated by non-selective cation conductances (Montell and Rubin, 1989) in the analysis of a fly mutant whose photoreceptors failed to retain a sustained response to maintained light stimuli. In mammals, TRP proteins were identified in most cases by their sequence homology. Nevertheless, some TRPs were identified by expression cloning, e.g., TRPV1 as the receptor for vanilloids such as capsaicin, or by positional cloning efforts to identify genes disrupted in human diseases, e.g., TRPML1 (also designated as mucolipin, MCOLN1, ML1) as a gene that is mutated in mucolipidosis type IV or TRPP2 (also designated as polycystin-2, PKD2, PC2) in autosomal polycystic kidney disease.

The mammalian 28 TRP proteins are classified according to structural homology into five subfamilies: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPML (mucolipin), and TRPP (polycystin; Montell et al., 2002; Clapham et al., 2005; Wu et al., 2010). All TRP channels are assumed to have six-transmembrane (6TM) polypeptide subunits that assemble as tetramers to form cation-permeable pores (Owsianik et al., 2006a).
Most TRP channels show little voltage dependence and are non-selective with a permeability for Ca$^{2+}$ over Na$^+$ (ratio $P_{Ca}/P_{Na}$) below 10. Therefore, TRP channels are not only important for Ca$^{2+}$ entry via the plasma membrane but play also an important role in electrogensis regulating the driving forces for Ca$^{2+}$ entry via other Ca$^{2+}$-permeable channels. Table 1 (Venkatachalam and Montell, 2007; Gees et al., 2010) gives an overview about the permeability of channels formed by individual TRP proteins, but it has to be emphasized that most of these information is based on studies of heterologously expressed channel proteins and the characteristics of those channels may differ significantly from native channel complexes existing in primary cells since the ectopically expressed channel proteins do not necessarily act in accordance with the native cellular context as in primary cells.

Transient receptor potentials are expressed in many (if not in all) excitable and non-excitable cells and are involved in sensing of a variety of environmental stimuli such as temperature, pH, osmolarity, pheromones, taste, and plant compounds. TRP channels participate in numerous cellular processes to determine organ and integrative body functions, and several mutations in Trp genes appear to be causative factors in rare heritable channelopathies (Freichel and Flockerzi, 2007; Nilius and Owsianik, 2010). Although the search for natural ligands and chemical modulators of TRP channels as therapeutics has been intensified in the last years, specific agonists or blockers are still lacking for most members of the TRP family until now. Therefore, genetic approaches are still required to advance a causal understanding of their physiological functions in primary cells, in organs, for systemic functions of organisms and for disease states. These approaches include over-expression of dominant-negative variants, antagonists oligonucleotides, and RNAi as well as targeted deletion of the gene of interest using homologous recombination (Freichel et al., 2011). Another obstacle that hinders the analysis of endogenous TRP channels is that specific antibodies are rare for most TRP proteins (Meissner et al., 2011) and, accordingly, this impedes investigations of the assembly and localization of TRP channels, but also the control of the effectiveness of RNAi approaches.

**EXPRESSION AND POSTULATED FUNCTIONS OF TRP PROTEINS IN MAST CELLS**

In the following we highlight key features regarding activation and functions of individual members of the TRP subfamilies, concerning their expression in mast cell models and established or postulated mast cell functions. Table 1 systematically summarizes information about the permeability, mode of activation, and the biological functions in native systems as revealed by mouse models for the individual mammalian TRP proteins. For more detailed information regarding structure, gating, special functional aspects of splice variants, TRP channelopathies, and citations of the wealth of original manuscripts about mammalian TRP proteins since their first description and functional characterization in 1995/1996 (Wes et al., 1995; Zhu et al., 1995; Philipp et al., 1996), we refer to various excellent recent review articles (Venkatachalam and Montell, 2007; Gees et al., 2010; Nilius and Owsianik, 2010; Wu et al., 2010). The current knowledge about the expression of TRP proteins in different cell lines and primary mast cell models (Table 2) is based on analysis using RT-PCR, gene arrays or quantitative PCR approaches as well as Western Blot analysis or immunocytochemistry for which commercial anti-TRP antibodies were used in most cases. For the latter approach, it has to be mentioned that many commercial suppliers pass the burden of antibody validation to the end user and that the specificity of the antibodies used was rarely tested rigorously in preparations of cells/tissues that do not express the target protein at all (Meissner et al., 2011). The functional role of individual TRP proteins in mast cells was analysed using TRP channel antagonists, RNAi approaches, and TRP deficient mouse models. Regarding RNAi approaches it needs to be noted that – despite the merits of this technology – off-target effects are not unusual, and were also described in a study where transfection of a $Trpm7$-specific siRNA achieved complete suppression of $Trpm7$ mRNA in other primary cells but also significantly reduced TRPM2 expression levels (Aarts et al., 2003). Secondly, the control of the effectiveness of RNAi approaches requires specific antibodies against the target TRP protein to avoid the situation that at the same time a poorly characterized RNAi experiment is controlled by non-validated antibodies and vice versa. Reports using mast cells derived from mice with targeted deletion of Trp genes are restricted until now to cells from mice with ubiquitous inactivation of individual Trp genes, in which the observed phenotype may be affected by compensatory mechanisms.

**TRPC CHANNELS**

The mammalian members of the TRPC family can be divided into three subfamilies on the basis of functional similarities and sequence homology: TRPC1/TRPC4/TRPC5, TRPC3/TRPC6/TRPC7, and TRPC2. Physical interaction between the TRPC family members was studied by co-immunoprecipitation and FRET experiments with heterologously expressed proteins and using immunoprecipitation from brain protein fraction using antibodies directed against peptides derived from TRPC proteins and revealed that TRPC1, TRPC4, and TRPC5 may coassemble as well as TRPC3, TRPC6, and TRPC7 (Lintschinger et al., 2006; Strubing et al., 2001; Goel et al., 2002; Hofmann et al., 2002). In embryonic rat brain, it was found that TRPC1, TRPC4, and TRPC5 interact with TRPC3 and TRPC6 (Strubing et al., 2003). All TRPC proteins seem to be activated by stimulation of G-protein-coupled receptors or receptor-tyrosine kinases. The activation of the PLC pathway leads to the opening of TRPC channels but in parallel to stimulation of IP3 receptors and subsequent depletion of intracellular Ca$^{2+}$ stores and, hence, SOCE. This raised the issue whether TRPC proteins are constituents of cation channels mediating SOCE, and a contribution of TRPC proteins to SOCE has been suggested very early after their first discovery (Hardie and Minke, 1993). In principle, over-expressed mammalian TRPCs have all been reported to be activated by store depletion (for review see, e.g., Venkatachalam et al., 2002). However, the dependence of TRPCs on store depletion requires special conditions. For instance, TRPC3 channels, which are activated directly by PLC-derived DAG in many expression systems, were also reported to be activated by reduction of the filling state of intracellular Ca$^{2+}$ stores (Kiselyov et al., 1998; Vazquez et al., 2003), but the ability of TRPC3 to contribute to SOCE was only found when it was expressed at low densities (Vazquez et al., 2003; Yildirim et al., 2005). The underlying cause for this phenomenon has not
Table 1 | Properties of channels formed by mammalian TRP proteins.

| Subtype  | Selectivity $P_{Ca^{2+}}/P_{Na^+}$ | Activation/modulation of activity | Consequences of TRP-deletion in mice |
|----------|-----------------------------------|----------------------------------|--------------------------------------|
| TRPC1    | $\sim 1$                          | PLC activation, store depletion, conformational coupling, mechanical stretch | Elevated body weight, impaired salivary gland fluid secretion |
| TRPC2    | $\sim 1$–$3$                      | PLC activation, diacylglycerol (DAG) | Abnormal sexual and mating behavior |
| TRPC3    | $\sim 1.5$                        | PLC activation, store depletion, conformational coupling, DAG, exocytosis | Defects in motor coordination and walking behavior |
| TRPC4    | $\sim 1$–$8$                      | PLC activation, store depletion (?), $P_{iP_{2}}$ breakdown, exocytosis | Impaired vascular function, altered 5-HT-mediated GABA release, defects in intestinal motility |
| TRPC5    | $\sim 2$–$9$                      | PLC activation, store depletion (?), sphingosine-1-phosphate, exocytosis | Decreased anxiety-like behavior |
| TRPC6    | $\sim 5$                          | PLC activation, conformational coupling, DAG, $P_{iP_{3}}$ | Grossly normal, increased artery contractility, impaired light response in intrinsically photosensitive retinal ganglion cells in TRPC6/TRPC7 compound KO mice |
| TRPC7    | $\sim 1$–$5$                      | PLC activation, store depletion, DAG | Impaired light response in intrinsically photosensitive retinal ganglion cells in TRPC6/TRPC7 compound KO mice |
| TRPV1    | $\sim 4$–$10$                     | Heat (43˚C), vanilloids, proinflammatory cytokines, protons, $P_{iP_{2}}$ | Reduced inflammatory hyperalgesia, impaired bladder function |
| TRPV2    | $\sim 1$–$3$                      | Heat (52˚C), osmotic cell swelling, exocytosis | Accelerated mortality in bacterial infection |
| TRPV3    | $\sim 1$–$10$                     | Warm (33–39˚C); PUFAs; menthol; compounds from oregano, cloves, and thymes | Impaired thermosensation, skin barrier effects, curved whiskers, and hair |
| TRPV4    | $\sim 6$                          | Warm (27–34˚C), osmotic cell swelling, 6’ 6’-EET, anandamide, 4aPDD, exocytosis | Altered body osmolarity; increased bone mass; impaired bladder function; reduced inflammatory hyperalgesia |
| TRPV5    | $>100$                            | Constitutively active$^1$, exocytosis (?) | Impaired renal $Ca^{2+}$ reabsorption; decreased bone thickness |
| TRPV6    | $>100$                            | Constitutively active$^1$, store depletion (?), exocytosis (?) | Impaired epididymal $Ca^{2+}$ absorption, male hypofertility, impaired $Ca^{2+}$ absorption |
| TRPM1    | $<1$                              | Translocation (?) | Impaired ON bipolar cell function and vision |
| TRPM2    | $\sim 0$, 3–$2$                   | ADP-ribose, cADP-ribose, pyrimidine nucleotides, arachidonic acid, NAD, $H_{2}O_{2}$, $Ca^{2+}$ | Impaired neutrophil infiltration in inflammation, increased ROS production in phagocytes |
| TRPM3    | $\sim 1$–$10^2$                   | Constitutively active$^1$, osmotic cell swelling, store depletion (?), $d$-erythro-sphingosine (?), pregnenolone sulfate | Impaired noxious heat perception |
| TRPM4    | Monovalent selective               | $Ca^{2+}$, voltage modulated, $P_{iP_{2}}$ | Increased release of inflammatory mediators from mast cell and cutaneous anaphylaxis; impaired dendritic cell migration; reduced secondary hemorrhage and lesions after spinal cord injury, hypertension associated with increased catecholamine release from chromaffin cells |
| TRPM5    | Monovalent selective               | Taste receptor activation (T1R, T2R), $Ca^{2+}$, voltage modulated, $P_{iP_{2}}$, heat (15–35˚C) | Impaired sweet, umami, and bitter taste reception; deflects in glucose-induced insulin release |
| TRPM6    | $<10^3$                           | $Mg^{2+}$ inhibited, translocation | Embryonic lethality, neural tube defects in development |
| TRPM7    | $\sim 0.2$–$2^3$                  | Activation mode of native channels unclear, $Mg^{2+}$ inhibited, ATP, protons, phosphorylation, $P_{iP_{2}}$ | Embryonic lethality; conditional TRPM7 deletion in T cells causes abnormal thymocyte development |
| TRPM8    | $\sim 0.3$–$4$                    | Cool (23–28˚C), menthol, icilin, pH modulated, $P_{iP_{2}}$ | Deficiencies in response to cold |
| TRPA1    | $\sim 0.8$–$5$                    | Cold (17˚C) (?), icilin, isothiocyanates, allicin (garlic), cannabinoids, bradykinin, PLC activation, DAG, PUFAs | Reduced response to noxious cold and intestine mechanical force |

(Continued)
been identified, but one explanation is that at high expression levels the transfected TRPCs titrate regulatory subunits that confer SOCE characteristics to TRPCs. Although numerous studies show that Orai 1 is the pore-forming subunit of store-operated channels (Lewis, 2007), a model with Orai as a regulatory subunit of SOCE function cannot necessarily be extrapolated across cell types. TRPC gating and function cannot necessarily be extrapolated across cell types.

TRPC3, TRPC6, and TRPC7 when expressed in heterologous systems are potentiated by Gq/11-coupled receptors or by direct application of diacylglycerol (DAG) analogs (Hofmann et al., 1999). Interestingly, the density of inward currents evoked by a DAG derivative were significantly higher in smooth muscle cells isolated from Trpc6−/− mice. This was explained by formation of TRPC3 homo-oligomeric channel complexes in TRPC6-deficient smooth muscle cells, because mRNA expression of Trpc3 appears to be up-regulated two- to threefold in cells of Trpc6−/− mice (Dietrich et al., 2005). This example demonstrates that the analysis of cation channels consisting of TRPC proteins is further aggravated by the fact that inactivation of a given TRP protein may be compensated by up- or down-regulation of other genes including physically or functionally interacting TRP genes. Time-dependent inactivation strategies may be used in such cases, or compound knock-out mice in which all redundant TRP proteins are inactivated simultaneously.

Trpc2 is a pseudogene in humans, but its rodent ortholog encodes a functional TRPC2 channel important to pheromone sensing in vomeronasal organ, where it can be directly activated by DAG (Lucas et al., 2003).

Expression of Trp genes was found in various types of mast cells (Table 2). TRPC1 has been detected in murine BMMC on mRNA (Sanchez-Miranda et al., 2010; Suzuki et al., 2010) and protein (Hernandez-Hansen et al., 2004) level, also in the rat cell line RBL-2H3 (Ma et al., 2008) and using a microarray expression analysis in human skin mast cells (Bradding et al., 2003). In RBL-2H3 cells, knockdown of TRPC1 and TRPC3 proteins through expression of corresponding shRNAs decreased the cells sensitivity to antigen-stimulation and shifted the Ca2+ wave initiation site from the tips of extended cell protrusions to the cell body (Cohen et al., 2009). Interestingly, in mice deficent for the Src

### Table 1 | Continued

| Subtype | Selectivity $P_{Ca^{2+}}/P_{Na^+}$ | Activation/modulation of activity | Consequences of TRP-deletion in mice |
|---------|----------------------------------|----------------------------------|-----------------------------------|
| TRPML 1 | Non-selective                    | Translocation with TRPP1, fluid flow, mechan-ical gating (?) | Lethal E13; embryonic cysts and extrarenal abnormalities including left-right asymmetry of visceral organs |
| TRPML 2 | Non-selective                    | Activation mode of native channels unclear, removal, and readdition of extracellular Na$^+$ | Vari-tint-waddler (Va) mice with a TRPML3 (A419P) gain of function mutation exhibit deafness, circling behavior, and pigmenta-tion defects |
| TRPML 3 | Non-selective                    | Activation mode of native channels unclear, potentiation by low pH | Motor deficits, retinal degeneration, decreased life span |
| TRPP2   | Non-selective                    | Activation mode of native channels unclear, potentiation by low pH | – |
| TRPP3   | Non-selective                    | Ca$^{2+}$, voltage modulated      | – |
| TRPP5   | Non-selective                    | Ca$^{2+}$, voltage modulated      | – |

1Not yet measured in primary cells; 2significant differences in individual splice variants; 3divalent cation selective (Ca$^{2+}$ and Mg$^{2+}$); 4localization primarily intracellularly in endolysosomes, permeability for Na$^+$, K$^+$, Ca$^{2+}$, Fe$^{2+}$, for more details see Cheng et al. (2010); 5localization primarily intracellularly in endolysosomes, permeability for Na$^+$, Ca$^{2+}$, K$^+$; for more details see Cheng et al. (2010).
Table 2 | Expression of TRP transcripts and proteins in mast cell models.

| Species | Cell type | Name | Method | Reference |
|---------|-----------|------|--------|-----------|
| TRPC1   | Mouse     | BMMC | qRT-PCR| Suzuki et al. (2010) |
|         | Mouse     | BMMC | RT-PCR | Sanchez-Miranda et al. (2010) |
|         | Rat       | RBL2H3 | RT-PCR, WB | Ma et al. (2008) |
|         | Mouse     | skin mast cells | Affymetrix gene array | Hernandez-Hansen et al. (2004) |
| TRPC2   | Rat       | RBL2H3 | RT-PCR | Ma et al. (2008) |
| TRPC3   | Mouse     | BMMC | RT-PCR | Sanchez-Miranda et al. (2010) |
|         | Mouse     | BMMC | WB     | Hernandez-Hansen et al. (2004) |
|         | Rat       | RBL2H3 | RT-PCR, WB | Ma et al. (2008) |
| TRPC4   | Mouse     | BMMC | qRT-PCR| Suzuki et al. (2010) |
|         | Mouse     | BMMC | WB     | Hernandez-Hansen et al. (2004) |
| TRPC5   | Mouse     | BMMC | qRT-PCR| Suzuki et al. (2010) |
|         | Mouse     | BMMC | RT-PCR | Sanchez-Miranda et al. (2010) |
|         | Rat       | RBL2H3 | RT-PCR, WB | Ma et al. (2008) |
| TRPC6   | Mouse     | BMMC | RT-PCR | Sanchez-Miranda et al. (2010) |
|         | Mouse     | BMMC | WB     | Hernandez-Hansen et al. (2004) |
|         | Mouse     | PB-3c | NB     | Buess et al. (1999) |
| TRPC7   | Rat       | RBL2H3 | RT-PCR | Ma et al. (2008) |
|         | Mouse     | BMMC | IP     | Sanchez-Miranda et al. (2010) |
| TRPV1   | Human     | HMC-1 | WB, RT-PCR | Zhang et al. (2011) |
|         | Human     | Mast cells in bladder | IHC | Lazzeri et al. (2004) |
|         | Rat       | RBL2H3 | RT-PCR | Stokes et al. (2004) |
| TRPV2   | Human     | HMC-1 | WB, RT-PCR | Zhang et al. (2011) |
|         | Human     | HMC-1 | RT-PCR | Kim et al. (2010) |
|         | Rat       | RBL2H3 | RT-PCR, WB, ICC, qPCR | Stokes et al. (2004) |
|         | Mouse     | P815 | NB, WB | Stokes et al. (2004) |
|         | Mouse     | BMMC | WB, (qPCR) | Stokes et al. (2004) |
|         | Rat       | RBL2H3 | NB, WB, ICC | Stokes et al. (2005) |
|         | Mouse     | P815 | NB, WB | Stokes et al. (2005) |
|         | Human     | HLMC | Affymetrix gene array | Bradding et al. (2003) |
|         | Human     | Skin mast cells | Affymetrix gene array | Bradding et al. (2003) |
|         | Human     | CBMC | Affymetrix gene array | Bradding et al. (2003) |
| TRPV3   | Not reported | | | |
| TRPV4   | Human     | HMC-1 | WB, RT-PCR | Zhang et al. (2011) |
|         | Human     | HMC-1 | RT-PCR | Kim et al. (2010) |
|         | Rat       | RBL2H3 | ICC | Yang et al. (2007) |
|         | Rat       | RBL2H3 | RT-PCR | Stokes et al. (2004) |
| TRPV5   | Not reported | | | |

(Continued)
family kinase Fyn expression of TRPC1 proteins was reduced by
∼30%, and cation currents, depolymerization of cortical F-actin
degranulation triggered by FcsRI-stimulation was signifi-
cantly reduced whereas mast cell degranulation evoked by ATP,
substance P, or thrombin was unaffected. Similar effects were
observed by downregulation of TRPC1 expression using siR-
NAs against TRPC1 and the deficits in FcsRI-triggered mast cell
activation could be rescued by exogenous expression of TRPC1
(Suzuki et al., 2010). \textit{Trpc2} mRNA has been reported in mouse
BMMC using RT-PCR (Ma et al., 2008). Expression of TRPC3 was
reported in mouse BMMC via Western Blot (Hernandez-Hansen
et al., 2004) and RT-PCR (Sanchez-Miranda et al., 2010) and with
both methods in the cell lines L138.8A and RBL-2H3 (Ma et al.,
2008). In BMMCs, transcripts of \textit{Trpc4} and \textit{Trpc5} (Suzuki et al.,
2010) and TRPC4 proteins (Hernandez-Hansen et al., 2004) were
found. TRPC5 transcript and protein expression was reported in
BMMCs (Ma et al., 2008). shRNA-mediated knock down of
TRPC5 in BMMCs was associated with a reduced Ca\textsuperscript{2+}
entry following depletion of intracellular Ca\textsuperscript{2+} stores and based on
over-expression experiments in these cells it was proposed that TRPC5
associates with Stim1 and Orai1 in a stoichiometric manner to
build Ca\textsuperscript{2+} and Sr\textsuperscript{2+} permeable channels that can be discrimi-
nated from channels made by Orai1 and Stim1 (Ma et al., 2008). How-
ever, receptor-mediated Ca\textsuperscript{2+} entry or membrane currents have
not been analysed in this study. \textit{Trpc6} and \textit{Trpc7} transcripts and
proteins were also found in mouse BMMC (Hernandez-Hansen

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Species & Cell type & Name & Method & Reference \\
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Species & Cell type & Name & Method & Reference \\
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TRPV CHANNELS

Similar to the TRPC family, the TRPV (vanilloid) family can be divided into two subfamilies on the basis of structure, function and Ca\(^{2+}\) selectivity: TRPV1-4, and TRPV5/6. In the TRPV subfamily, TRPV5 and TRPV6 can form heteromeric channel complexes (Hoenderop et al., 2003b; Hellwig et al., 2005; Schaefer, 2005). Furthermore, TRPV1 can associate with TRPV2 and TRPV3 (Cheng et al., 2007) and widespread interaction has been shown for TRPV1-TRPV4 (Cheng et al., 2007).

TRPV1, TRPV2, TRPV3, and TRPV4 are non-selective channel proteins that are activated by a different range in temperatures, respectively, and by various other stimuli (Table 1). In addition, TRPV1 could be activated by low pH (Caterina et al., 1997; Jordt et al., 2000) and by vanilloid compounds, such as capsaicin and capsinate found in hot (chili) and non-pungent (bell) peppers, respectively (Caterina et al., 1997; Iida et al., 2003).

TRPV2 (like TRPV4) is activated by osmotic cell swelling and has a critical role in macrophage particle binding and phagocytosis (Link et al., 2010). TRPV3 is activated by a variety of botanical compounds (Moqrich et al., 2005). TRPV4 is sensitive to osmotic and mechanical stimuli, such as cell swelling or fluid flow. It could be activated by arachidonic acid metabolite 5\(^{′}-\)6\(^{′}\)-epoxyeicosatrienoic acid (5\(^{′}-\)6\(^{′}\)-EET; Vriens et al., 2005) or by 4\(^{α}\)-Phorbol 12,13-Didecanoate (Watanabe et al., 2002).

TRPV5 and TRPV6 are the only highly Ca\(^{2+}\)-selective channels in the TRP channel family. They are not heat-sensitive and tend to be active at low [Ca\(^{2+}\)]\(_i\) concentrations and physiologically regulated in highly metastatic melanoma cells (Duncan et al., 1998). TRPM1 proteins reside in intracellular organelles and do not reach the plasma membrane upon heterologous expression, but form non-selective currents when expressed in SK-Mel22a melanoma cells (Oancea et al., 2009). TRPM1 is activated by the mGluR6 signaling cascade and thus is required for the depolarizing light response in ON bipolar cells (Morgans et al., 2009) and mutations in the Trpm1 gene are associated with congenital stationary night blindness (CSNB) disease in humans (Li et al., 2009).

TRPM3 proteins are able to form constitutively active cation channels. Various splice variants are expressed from the Trpm3 gene with TRPM3\(\alpha 1\) being poorly permeable for divalent cations, whereas TRPM3\(\alpha 2\)-induced channels conduct Ca\(^{2+}\) and Mg\(^{2+}\). The steroid hormone pregnenolone sulfate may act as endogenous ligand for TRPM3 (Wagner et al., 2008).

TRPM2 is activated by ADP-ribose (EC\(_{50}\), 100 \(\mu\)M) and activated by H\(_2\)O\(_2\) and under conditions of ROS production (Hara et al., 2002; Perraud et al., 2005), and deletion of Trpm2 leads to decreased reactive oxygen species-induced chemokine production in monocytes (Yamamoto et al., 2008). Recently, Di et al. (2011) showed that deletion of Trpm2 increases ROS production in phagocytes and introduced the concept that TRPM2-mediated cation entry and subsequent membrane depolarization functions...
as an inhibitory feedback mechanism for ROS production in these cells.

TRPM4 and TRPM5 are (together with TRPM3α1) the only monovalent-selective ion channels of the TRP family (Launay et al., 2002; Hofmann et al., 2003). TRPM4, but not TRPM5, is inhibited by intracellular ATP, whereas TRPM5 is inhibited by intracellular acidic pH. Both are activated by an increase in Ca\(^{2+}\) levels in the cytosol, but the sensitivity to [Ca\(^{2+}\)]\(_i\) as determined by different research groups varies greatly (Vennekens and Nilius, 2007). Studies in Trpm4\(^{-/-}\) mice reveal a critical role for TRPM4 proteins in mast cell activation (see below). Moreover, these mice exhibited high blood pressure due to elevated release of catecholamines (Mathar et al., 2010).

TRPM6 and TRPM7 are unique among ion channels because they possess both ion channel and protein kinase activities. Channels formed by these proteins allow Mg\(^{2+}\) and Ca\(^{2+}\) entry into the cell and are inhibited by intracellular Mg\(^{2+}\) (0.3–1.0 mM; Nadler et al., 2001; Voets et al., 2004b). TRPM6 is primarily expressed in kidney and intestine, where it has been suggested to be responsible for epithelial Mg\(^{2+}\) reabsorption (Schlingmann et al., 2002). TRPM7 is ubiquitously expressed and deletion of the Trpm7 gene leads to embryonic lethality (Jin et al., 2008; Weissgerber et al., 2008).

Like TRPM1, TRPM8 was originally identified in a screen of cancer-related genes (Tsavaler et al., 2001). It can be activated by cold (8–28°C) and enhanced by cooling compounds such as menthol and icilin (McKemy et al., 2002) and Trpm8\(^{-/-}\) mice show deficits in their ability to discriminate between cold and warm surfaces (Bautista et al., 2007). Temperature modulates the voltage dependence of the channel, and menthol and icilin mimick this effect (Voets et al., 2004a).

Expression of TRPM1, TRPM3, TRPM5, and TRPM6 has not been reported in mast cell models, while the other members of TRPM subfamily play important roles in mast cell functions. Trpm2 transcripts were identified in human lung mast cells and cord blood derived mast cells in a microarray expression analysis (Bradding et al., 2003). In mouse BMMC, Trpm4 transcripts were detected using Northern blot analysis and the 138 kDa TRPM4 proteins were identified in BMMCs of wild type but not of Trpm4\(^{-/-}\) mice (Vennekens et al., 2007). After preabsorption of the same anti-TRPM4 antibody using microsomal membrane protein fractions from BMMCs of TRPM4\(^{-/-}\) mice a specific staining of TRPM4 proteins in connective tissue mast cells in skin sections could be achieved. TRPM4 proteins, similarly like TRPM5 proteins, act as Ca\(^{2+}\)-activated non-selective cation channels and critically determine the driving force for Ca\(^{2+}\) influx into cells (Launay et al., 2004). It could be shown that TRPM4 channels depolarize the membrane following adenosine- and FcεRI-stimulation and, thereby, critically decrease the Ca\(^{2+}\) influx in BMMCs via CRAC channels. Accordingly, activated Trpm4\(^{-/-}\) BMMCs release excessive histamine, leukotrienes and tumor necrosis factor (TNF), and Trpm4\(^{-/-}\) animals display a more severe acute anaphylactic response in the skin compared to wild-type controls indicating that TRPM4 channel activation is an efficient mechanism for limiting antigen-induced mast cell activation (Vennekens et al., 2007). Additionally, antigen- and SCF-induced migration of BMMCs is largely diminished in the absence of TRPM4, and F-actin formation is reduced in DNP-HSA-stimulated BMMCs from Trmp4\(^{-/-}\) mice (Shimizu et al., 2009). At this point it has to be mentioned that the increased [Ca\(^{2+}\)]\(_i\), elevation observed upon FcεRI-stimulation in TRPM4-deficient mice led to increased release of TNF-α but not of IL-6. It is known, that release of both mast cell mediators is calcium-dependent, but an explanation for this difference may be that transcription and/or production of IL-6 may already be saturated under these conditions of FcεRI-stimulation and could not be further stimulated by the additional increase of [Ca\(^{2+}\)]\(_i\) in TRPM4-deficient BMMCs.

Expression of TRPM7 has been found in human lung mast cells and the human cell line LAD-2 (Wykes et al., 2007) as well as in RBL-2H3 cells (Stokes et al., 2004) and Mg\(^{2+}\)-inhibited currents (MIC), which can be mediated by TRPM7 proteins, were identified in RBL-2H3 cells, HMC-1 cells, and human lung mast cells. Downregulation of TRPM7 expression in HMC-1 cells and human lung mast cells resulted in significant reduction of MIC currents and mast cell survival which could not be rescued by an increase in the extracellular Mg\(^{2+}\) concentration (Wykes et al., 2007). In addition, TRPM7 currents in RBL-2H3 cells might be involved in Ca\(^{2+}\) and Mg\(^{2+}\) entry during cell cycle regulation since it could be shown that MIC currents were strongly upregulated specifically in the G1 phase of the cell cycle to meet cellular demands for Ca\(^{2+}\) and/or Mg\(^{2+}\) fluxes during this stage of cell division (Tani et al., 2007). Trpm7-deficient mice as well as mice homozygous for an allele lacking the kinase domain of TRPM7 (Trpm7\(\Delta kinase/\Delta kinase\)) die early during development (Jin et al., 2008; Weissgerber et al., 2008; Ryazanova et al., 2010), but Trpm7\(^{+/-}\)/\(\Delta kinase\) are viable and MIC currents are significantly reduced in PMCs of these mice (Ryazanova et al., 2010). However, the consequences of MIC current reduction for mast cell activation have not been reported so far.

TRPM8 proteins, which form Ca\(^{2+}\)-conducting cation channels activated by menthol or cold, have also been proposed as mediators of mast cell activation, e.g., in the development of cold urticaria. However, Medic et al. (2011) found no deficits in mast cell activation using Ca\(^{2+}\) imaging, mast cell degranulation and development of passive anaphylaxis in Trpm8\(^{-/-}\) mice, which makes a role of TRPM8 for mast cell activation in cold urticaria unlikely.

**TRPA1 CHANNELS**

TRPA1 is the only member of the TRPA (ankyrin) family characterized by the 14 amino-terminal ankyrin repeats (Story et al., 2003). Its expression in hair cells led to the hypothesis that it forms an auditory mechanotransduction channel (Corey et al., 2004), but this concept could not be supported sufficiently as, e.g., Trpa1\(^{-/-}\) mice exhibit no overt vestibular deficits and auditory responses are completely normal (Bautista et al., 2006; Kwan et al., 2006). TRPA1 was reported to be activated by noxious cold but the thermosensitivity (Story et al., 2003; Corey et al., 2004) of TRPA1 is also debated. TRPA1 is activated by various chemicals (Bandell et al., 2004) including allyl isothiocyanate (the pungent compound in mustard oil), allicin (from garlic),
cinnamaldehyde (from cinnamon), menthol (from mint), tetrahydrocannabinol (from marijuana), nicotine (from tobacco), and bradykinin (see Table 1). Recently it was reported that protein kinase A/phospholipase C-mediated trafficking to the plasma membrane contributes to TRPA1 activation (Schmidt et al., 2009). TRPA1 has been detected in mast cells so far, but in resting mast cells it was predominantly localized in intracellular vesicular structures and interacts with secretogranin III, a protein involved in secretory granule biogenesis in mast cells, implicating that TRPA1 might play an alternative role to the regulation of cation entry across the plasma membrane in mast cells compared to other cell types (Turner et al., 2007; Prasad et al., 2008).

**TRPML and TRPP Channels**

The TRPML (mucolipin) family contains three mammalian members: TRPML1, TRPML2, and TRPML3. The TRPML proteins show only low homology with the other TRP channels and are comparatively shorter. Heterologously expressed TRPML proteins can interact with each other (Venkatachalam et al., 2006; Curcio-Morelli et al., 2010). Trpm1 was first identified by a positional cloning strategy as the gene mutated in patients suffering from Mucolipidosis type IV (MLIV; Bargal et al., 2000), TRPML3 was discovered as the channel mutated in varitint-waddler mice, characterized by a variegated coat color, vestibular defects, hyperactivity, and embryonic lethality (Xu et al., 2007). TRPML1 and TRPML2 are ubiquitously expressed and localize primarily to the lysosomal and late endosomal compartments (Manzioni et al., 2004; Puertollano and Kiselyov, 2009). Recently, Dong et al. developed a method allowing the measurement of ion currents directly in endolysosomes. This was achieved by treatment of the cells with Vacuolin-1, leading to an increase of diameter of the endolysosomes. This was achieved by treatment of the cells with Vacuolin-1.

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**MECHANISMS: HOW TRP CHANNELS REGULATE CHANGES IN \([\text{Ca}^{2+}]\), AND MAST CELL ACTIVATION**

Taken together, TRP channels were found to influence cellular \([\text{Ca}^{2+}]\) signaling by several mechanisms. First, by conducting \([\text{Ca}^{2+}]\) ions to various degrees TRP channels directly contribute to \([\text{Ca}^{2+}]\) influx via the plasma membrane. TRP channels with high calcium selectivity are TRPV5 and TRPV6 (Vennekens et al., 2000), but also non-selective TRP channels composed of, e.g., TRPC1 (Suzuki et al., 2010) or TRPC5 (Ma et al., 2008) may contribute in this way. Second, by conducting \([\text{Na}^{+}]\) TRP channels mediate electrogenic effects through plasma membrane depolarization which may have opposite consequence in different cell types: in contrast to excitable cells, where TRP-mediated \([\text{Na}^{+}]\) entry and depolarization can enhance \([\text{Ca}^{2+}]\) entry by gating of voltage-operated \([\text{Ca}^{2+}]\) channels (Tvilovskyy et al., 2009), they can do the opposite in non-excitable cells such as mast cells; here a significant part of stimulated \([\text{Ca}^{2+}]\) entry enters the cell via inwardly rectifying CRAC channels, and TRP-mediated \([\text{Na}^{+}]\) entry and subsequent depolarization reduces the driving force for \([\text{Ca}^{2+}]\) entry by shifting the membrane potential toward more positive potentials (Vennekens et al., 2007). A counteracting mechanism by a \([\text{Ca}^{2+}]\) activated \([\text{K}^{+}]\) channel leading to membrane hyperpolarization and an increase of the driving force for \([\text{Ca}^{2+}]\) entry following FcεRI-stimulation was shown for SK4 (KCa3.1) proteins (Shumilina et al., 2008) emphasizing the relevance of this regulatory principle for adjusting \([\text{Ca}^{2+}]\); and activation of mast cells. Third, TRP channels can be activated or inhibited by themselves by \([\text{Ca}^{2+}]\) which further contributes to the complexity of regulation of \([\text{Ca}^{2+}]\); TRP channels that are activated by \([\text{Ca}^{2+}]\) include TRPC1, TRPC4, TRPC5, TRPC6, TRPV4, TRPM2, TRPA1, TRPM4, and TRPM5. Also many TRP channels are modulated by \([\text{Ca}^{2+}]\) via complex signaling cascades including \([\text{Ca}^{2+}]\)/calmodulin binding, \([\text{Ca}^{2+}]\)-dependent modulation of phospholipase C, and \([\text{Ca}^{2+}]\)-dependent activation of PKC. Fourth, there is emerging evidence that several TRP channels are also located in the membrane of the sarco/endooplasmic reticulum (SR/ER), endosomes, lysosomes, or other intracellular vesicles where they can serve as \([\text{Ca}^{2+}]\) release channels and conduct \([\text{Ca}^{2+}]\) from the luminal stores into the cytoplasm which may affect specific mast cell functions; for instance, it was reported that TRPV1, TRPM8, and TRPP2 can form \([\text{Ca}^{2+}]\)-conducting channels in the SR/ER, and TRPML1, TRPM2, and TRPV2 may function as \([\text{Ca}^{2+}]\)-release channels in endo-/lysosomes (for more details see Dong et al., 2010; Gees et al., 2010). Finally, it has to be considered that many studies about \([\text{Ca}^{2+}]\)-dependent mast cell functions analysed measurements of global cytoplasmic \([\text{Ca}^{2+}]\) concentration rather than the nature of the \([\text{Ca}^{2+}]\) signals, e.g., differences in the frequency of transient episodic \([\text{Ca}^{2+}]\) elevations (\([\text{Ca}^{2+}]\) spikes/oscillations) and subcellular localization and direction of \([\text{Ca}^{2+}]\) signals such as \([\text{Ca}^{2+}]\) waves which may be crucial for distinct mast cell functions. In this line, a threshold of \([\text{Ca}^{2+}]\) elevation in the vicinity of store-operated...
Ca\(^{2+}\) channels is apparently necessary to induce nuclear NFAT translocation as a parameter for activation of gene expression (Kar et al., 2011, 2012). In this case the signal triggered by this localized translocation as a parameter for activation of gene expression (Kar et al., 2011, 2012).

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