frontiers in
IMMUNOLOGY

REVIEW ARTICLE
published: 12 June 2012
doi: 10.3389/fimmu.2012.00150

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-excitable 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

CA^{2+} ENTRY PATHWAYS AND MAST CELL ACTIVATION

In mast cells, the increase of free cytosolic Ca^{2+} regulates a variety of cellular processes including degranulation with release of preformed inflammatory mediators (Ozawa et al., 1993), production of eicosanoids such as leukotrienes (Chang et al., 2006), activation of transcription factors including the nuclear factor of activated T cells (NFAT; Kar et al., 2011), and synthesis of cytokines (Plaut et al., 1989) as well as cytoskeletal rearrangements required for migration of mast cells and chemotaxis (Hartmann et al., 1997). Mast cell derived mediators can evoke both pathological inflammatory responses in allergic or autoimmune diseases but they can also have protective functions, e.g., by induction of innate immune responses leading to clearance of pathogens or by degrading endogenous and exogenous toxins (Marshall, 2004; Galli et al., 2005; Metz and Maurer, 2007). The importance of extracellular Ca^{2+} as a requirement for anaphylactic release of histamine from rat peritoneal mast cells was already shown in 1972 (Foreman and Mongar, 1972), and it could be shown that Ca^{2+} could be replaced by Sr^{2+} or Ba^{2+} to achieve mast cell degranulation (Foreman et al., 1977). Later, it was shown that substantial amounts of Ca^{2+} in the external medium (i.e., $>50\,\mu M$) was absolutely required for degranulation in rat basophilic leukemia (RBL)-2H3 cells (Beaven et al., 1984) leading to the concept that antigen-mediated mast cells degranulation is dependent on Ca^{2+} influx through Ca^{2+} channels that are permeable for Sr^{2+}/Ba^{2+} (Ma and Beaven, 2009, 2011). Distinct temporal and spatial patterns of the increase in intracellular Ca^{2+} concentration triggered by individual Ca^{2+} mobilizing mast cell activators may explain the specificity of mast cell responses. For example, differences in the amplitude and duration of Ca^{2+} signals in response to different stimulants differentially influence histamine secretion or production of eicosanoids (van Haaster et al., 1995). Also, it was shown that, under certain conditions, mast cells can be stimulated to undergo chemotaxis without degranulation (Taub et al., 1995). More recent work has revealed that a range of mast cell responses are activated by spatially restricted Ca^{2+} signals just below the plasma membrane (Di Capite and Parekh, 2009; Kar et al., 2011).

Although mast cells have numerous functions beyond the development of allergies, studies of mast cell signal transduction have mainly been driven by the central role of these cells in allergic inflammatory responses (Metcalfe et al., 1997). The manifestations of mast cell-driven allergic reactions are considered to be mainly a consequence of the release of pro-inflammatory mediators following antigen-induced aggregation of high-affinity receptors for IgE (FcεRI), expressed at the mast cell surface. FcεRI cross-linking activates a large number of signaling molecules (Blank and Rivera,

2004; Gilfillan and Tkaczyk, 2006). A major downstream target is phospholipase Cγ1 (PLCγ1), which catalyzes the hydrolysis of phosphatidylinositol (4,5) bisphosphate (PIP_2) to diacylglycerol (DAG) and inositol (1,4,5) trisphosphate (IP_3). DAG and IP_3 promote protein kinase C (PKC) activation and release of Ca^{2+} from intracellular stores, respectively, followed by an influx of Ca^{2+} from the extracellular space. Also in other non-excitable cells the depletion of intracellular Ca^{2+} stores correlates with influx of Ca^{2+} from the extracellular space suggesting that the amount of Ca^{2+} in the stores controls the extent of Ca^{2+} influx, a process that was called store-operated Ca^{2+} entry (SOCE) or capacitative Ca^{2+} entry (CCE; Putney, 1986; Parekh and Putney, 2005) and described later also in mast cells (Putney, 1986; Ali et al., 1994; Falcone and Fewtrell, 1995). Ionic currents mediating this Ca^{2+} influx were first characterized by Hoth and Penner (1992, 1993) in RBL cells and rat peritoneal mast cells. The physiological hallmark of the underlying channel is a high selectivity for Ca^{2+} over other cations and its activation by depletion of intracellular Ca^{2+} stores, e.g., by IP_3 and chelation of cytosolic Ca^{2+}. The Ca^{2+} selectivity of Ca^{2+} release activated Ca^{2+} (CRAC) channels is similar to that of voltage-activated Ca^{2+} channels (VDCC) which were shown to be expressed and to modulate mast cell activation (Yoshimaru et al., 2009), but the conductance of CRAC channels is much lower. Also, replacement of external Ca^{2+} with Sr^{2+} or Ba^{2+} resulted in a decline in I_{CRAC} activity (Zweifach and Lewis, 1996) indicating that CRAC channels cannot represent the exclusive Ca^{2+} entry channel mediating Ca^{2+} dependent mast cell degranulation. The desire to identify the molecular nature of SOCE was and still is the motivation for many workers to characterize mammalian transient receptor potential (TRP) channels. However, the pore properties of most TRP channels that have been studied in detail, including TRPV6, which was identified 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 Owsianik 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 stromal interaction molecule 1 (Stim1) was shown to represent the Ca^{2+} sensor coupling the process of depletion of intracellular Ca^{2+} stores with Ca^{2+} influx across the plasma membrane through CRAC channels (Lewis, 2007). Orai1 and its homologs Orai2 and Orai3 were shown to be expressed in RBL-2H3 cells and bone marrow-derived mast cells (BMMCs; Gross et al., 2007). SOCE is substantially decreased in *Orai1*-deficient BMMCs (Gwack et al., 2008), and the FcεRI-mediated Ca^{2+} entry is reduced by 70%, while the cells completely lack detectable Ca^{2+} (CRAC) currents (Vig et al., 2008). Interestingly, in this study it was concluded that Ca^{2+} release from intracellular stores is unchanged in *Orai1*-deficient BMMCs (Vig et al., 2008) suggesting that ORAI1 proteins are non-critical components for the refilling of these Ca^{2+} stores. The relative contribution of Orai2 and Orai3 for Ca^{2+} entry in mast cells is still unclear. Although these results support the conclusion that ORAI1 (CRACM1)-proteins build the Ca^{2+}-selective channels responsible for the majority of Ca^{2+} entry into mast cells, there is still some residual Ca^{2+} entry in *Orai1*-deficient BMMCs after stimulation of the FcεRI or store depletion. Ca^{2+} entry in *Orai1*-deficient mast cells following activation with other Ca^{2+} mobilizing mast cell activators has not been analysed so far. This suggests that other channel proteins – especially members of the TRP family such as TRPC5 (Ma et al., 2008) – might contribute to Ca^{2+} entry either as part of an Orai/TRP channel complex (Liu et al., 2003, 2007; Liao et al., 2007; Yuan et al., 2007) or independently.

In addition to activation of FcεRI and depletion of intracellular Ca^{2+} stores there is increasing evidence that receptors for other ligands such as adenosine, endothelin-1, stem cell factor (SCF), lysophosphatidylcholine (LPC), sphingosine-1 phosphate (S1P), substance P, and others, which markedly influence mast cell activation in a physiological setting, do also induce elevations of $[Ca^{2+}]_i$. These receptors can either potentiate FcεRI-mediated mast cell activation or, by themselves, stimulate the release of mast cell mediators. The pathways leading to elevation of $[Ca^{2+}]_i$ following stimulation of these receptors are still poorly characterized, and particularly it is not known whether or to which degree the resultant receptor-activated Ca^{2+} entry is mediated by store depletion. Receptor stimulation using substance P or compound 48/80 leads to a Ca^{2+} influx through non-selective cation channels in rat peritoneal mast cells (Penner et al., 1988; Kuno and Kimura, 1992; Fasolato et al., 1993). Recently, an additional mechanism for regulation of Ca^{2+} entry in mast cells has been discovered that does not rely on mast cell intrinsic mechanisms such as receptor stimulation by soluble mediators or regulation of the driving force for Ca^{2+} entry but on the interaction with another cell type: it could be shown that binding of OX40 expressed on regulatory T cells to the mast cell based receptor OX40L inhibits Ca^{2+} entry by an increase of intracellular cAMP levels in mast cells (Gri et al., 2008). The molecular constituents of the Ca^{2+} conducting channels regulated by this new pathway are unknown like those channels activated by the numerous Ca^{2+} mobilizing agonists described above, but members of the TRP family are potential candidates also for these Ca^{2+} entry pathways.

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 through strikingly diverse mechanisms. The first TRP channel gene was discovered in *Drosophila melanogaster* (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 six 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 electrogenesis 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, antisense 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., 2000; 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 IP_3 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_{Ca2+}/P_{Na+}	Activation/modulation of activity	Consequences of TRP-deletion in mice
TRPC1	∼1	PLC activation, store depletion, conformational coupling, mechanical stretch	Elevated body weight, impaired salivary gland fluid secretion
TRPC2	∼1–3	PLC activation, diacylglycerol (DAG)	Abnormal sexual and mating behavior
TRPC3	∼1.5	PLC activation, store depletion, conformational coupling, DAG, exocytosis	Defects in motor coordination and walking behavior
TRPC4	∼1–8	PLC activation, store depletion (?), PIP_2 breakdown, exocytosis	Impaired vascular function, altered 5-HT-mediated GABA release, defects in intestinal motility
TRPC5	∼2–9	PLC activation, store depletion (?), sphingosine-1-phosphate, exocytosis	Decreased anxiety-like behavior
TRPC6	∼5	PLC activation, conformational coupling, DAG, PIP_3	Grossly normal, increased artery contractility, impaired light response in intrinsically photosensitive retinal ganglion cells in TRPC6/TRPC7 compound KO mice
TRPC7	∼1–5	PLC activation, store depletion, DAG	Impaired light response in intrinsically photosensitive retinal ganglion cells in TRPC6/TRPC7 compound KO mice
TRPV1	∼4–10	Heat (43˚C), vanilloids, proinflammatory cytokines, protons, PIP_2	Reduced inflammatory hyperalgesia, impaired bladder function
TRPV2	∼1–3	Heat (52˚C), osmotic cell swelling, exocytosis	Accelerated mortality in bacterial infection
TRPV3	∼1–10	Warm (33–39˚C); PUFAs; menthol; compounds from oregano, cloves, and thymes	Impaired thermosensation, skin barrier effects, curved whiskers, and hair
TRPV4	∼6	Warm (27–34˚C), osmotic cell swelling, 5′ 6′-EET, anandamide, 4αPDD, 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	∼0, 3–2	ADP-ribose, cADP-ribose, pyrimidine nucleotides, arachidonic acid, NAD, H_2O_2, Ca^{2+}	Impaired neutrophil infiltration in inflammation, increased ROS production in phagocytes
TRPM3	∼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, PIP_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, PIP_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	∼0.2–2[3]	Activation mode of native channels unclear, Mg^{2+} inhibited, ATP, protons, phosphorylation, PIP_2	Embryonic lethality; conditional TRPM7 deletion in T cells causes abnormal thymocyte development
TRPM8	∼0.3–4	Cool (23–28˚C), menthol, icilin, pH modulated, PIP_2	Deficiencies in response to cold
TRPA1	∼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)

Table 1 | Continued

Subtype	Selectivity P_{Ca2+}/P_{Na+}	Activation/modulation of activity	Consequences of TRP-deletion in mice
TRPML 1	[4]	Activation mode of native channels unclear, potentiation by low pH	Motor deficits, retinal degeneration, decreased life span
TRPML 2	[4]	Activation mode of native channels unclear, potentiation by low pH	–
TRPML 3	[5]	Activation mode of native channels unclear, removal, and readdition of extracellular Na^+	Varitint-waddler (Va) mice with a TRPML3 (A419P) gain of function mutation exhibit deafness, circling behavior, and pigmentation defects
TRPP2	Non-selective	Translocation with TRPP1, fluid flow, mechanical gating (?)	Lethal E13; embryonic cysts and extrarenal abnormalities including left-right asymmetry of visceral organs
TRPP3	∼1–10	Ca^{2+}, voltage modulated	–
TRPP5	non-selective	?	–

[1]Not yet measured in primary cells; [2]significant differences in individual splice variants; [3]divalent cation selective (Ca^{2+} and Mg^{2+}); [4]localization primarily intracellularly in endolysosomes, permeability for Na^+, K^+, Ca^{2+}, Fe^{2+}, for more details see Cheng et al. (2010); [5]localization primarily intracellularly in endolysosomes, permeability for Na^+, Ca^{2+}, K^+; for more details see Cheng et al. (2010).

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 Orai1 is the pore-forming subunit of store-operated channels (Lewis, 2007), a model with Orai as a regulatory subunit of SOCE channels composed of pore-forming TRPC subunits has recently been proposed (Liao et al., 2008). Additionally, Stim1 was found to hetermultimerize TRPC proteins either directly (TRPC1, TRPC4, TRPC5) or indirectly (TRPC3, TRPC6) to determine their store-operated activation mode (Yuan et al., 2007, 2009). Taken together, the question of whether and how TRPC proteins contribute to SOCE remains highly controversial (Parekh, 2010) and cannot be generally answered but may depend on the relative expression of the above mentioned and/or not yet identified constituents that make up SOC channel complexes in individual cell types.

The permeability (P_{Ca}/P_{Na}) of channels formed by heterologously expressed TRPC proteins varies between 1 and 10 (**Table 1** and Venkatachalam and Montell, 2007; Gees et al., 2010). Whether TRPC1 can form functional homomeric channels by itself still remains debatable. TRPC1 forms heteromeric channels with TRPC4 or TRPC5, which have properties distinct from those of homomultimers (Strubing et al., 2001). TRPC4 and TRPC5 share many structural and functional characteristics such as the activation by $G_{q/11}$-coupled receptors. On the other hand there are considerable discrepancies regarding the precise activation mechanism in response to PLC stimulation and with respect to their channel properties (e.g., permeability), even if homomeric TRPC proteins are analyzed (Cavalie, 2007). The differences may result from the expression system used and thereby emphasize the need to analyze the action of individual TRPC proteins in the context of their native environment. This can be exemplified by studies in mice with inactivation of the *Trpc4* gene. Depending on the cell type studied, channels with completely different characteristics are impaired in *Trpc4*-deficient mice: deletion of the *Trpc4* gene results in 95% reduction of acetylcholine (ACh)-triggered store-operated channels with a Ca^{2+} over Na^+ selectivity of >100 in endothelial cells whereas in ileal smooth muscle cells the loss of TRPC4 leads to an 80% reduction of ACh-evoked currents which are predominantly carried by Na^+ and activated by PIP_2 breakdown rather than by store depletion (Freichel et al., 2001; Tsvilovskyy et al., 2009). These results show that TRPC gating and function cannot necessarily be extrapolated across cell types.

TRPC3, TRPC6, and TRPC7 when expressed in heterologous systems are potentiated by $G_{q/11}$-coupled receptors or by direct application of diacylglycerol (DAG) analogs (Hofmann et al., 1999). Interestingly, the density of inward currents evoked by a DAG derivate 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 *Trpc* 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 Ca^{2+} wave initiation site from the tips of extended cell protrusions to the cell body (Cohen et al., 2009). Interestingly, in mice deficient for the Src

Table 2 | Expression of TRP transcripts and proteins in mast cell models.

Species	Cell type	Name	Method	Reference
TRPC1				
Mouse	Primary cells	BMMC	qRT-PCR	Suzuki et al. (2010)
Mouse	Primary cells	BMMC	RT-PCR	Sanchez-Miranda et al. (2010)
Rat	Cell line	RBL-2H3	RT-PCR, WB	Ma et al. (2008)
Mouse	Primary cells	BMMC	WB	Hernandez-Hansen et al. (2004)
Human	Primary cells	skin mast cells	Affymetrix gene array	Bradding et al. (2003)
TRPC2				
Rat	Cell line	RBL-2H3	RT-PCR	Ma et al. (2008)
TRPC3				
Mouse	Primary cells	BMMC	RT-PCR	Sanchez-Miranda et al. (2010)
Mouse	Primary cells	L138.8A	qRT-PCR	Sel et al. (2008)
Rat	Cell line	RBL-2H3	RT-PCR, WB	Ma et al. (2008)
Mouse	Primary cells	BMMC	WB	Hernandez-Hansen et al. (2004)
TRPC4				
Mouse	Primary cells	BMMC	qRT-PCR	Suzuki et al. (2010)
Mouse	Primary cells	BMMC	WB	Hernandez-Hansen et al. (2004)
TRPC5				
Mouse	Primary cells	BMMC	qRT-PCR	Suzuki et al. (2010)
Mouse	Primary cells	BMMC	RT-PCR	Sanchez-Miranda et al. (2010)
Rat	Cell line	RBL-2H3	RT-PCR, WB	Ma et al. (2008)
TRPC6				
Mouse	Primary cells	BMMC	RT-PCR	Sanchez-Miranda et al. (2010)
Mouse	Primary cells	BMMC	WB	Hernandez-Hansen et al. (2004)
Mouse	Cell line	PB-3c	NB	Buess et al. (1999)
TRPC7				
Rat	Cell line	RBL-2H3	RT-PCR	Ma et al. (2008)
Mouse	Primary cells	BMMC	IP	Sanchez-Miranda et al. (2010)
TRPV1				
Human	Cell line	HMC-1	WB, RT-PCR	Zhang et al. (2011)
Human	Mast cells in bladder		IHC	Lazzeri et al. (2004)
Rat	Cell line	RBL-2H3	RT-PCR	Stokes et al. (2004)
Human	Skin mast cells		IHC	Stander et al. (2004)
TRPV2				
Human	Cell line	HMC-1	WB, RT-PCR	Zhang et al. (2011)
Human	Cell line	HMC-1	RT-PCR	Kim et al. (2010)
Rat	Cell line	RBL-2H3	RT-PCR, NB, WB, ICC, qPCR	Stokes et al. (2004)
Mouse	Cell line	P815	NB, WB	Stokes et al. (2004)
Mouse	Primary cells	BMMC	WB, (qPCR)	Stokes et al. (2004)
Rat	Cell line	RBL-2H3	NB, WB, ICC	Stokes et al. (2005)
Mouse	Cell line	P815	NB, WB	Stokes et al. (2005)
Human	Primary cells	HLMC	Affymetrix gene array	Bradding et al. (2003)
Human	Primary cells	Skin mast cells	Affymetrix gene array	Bradding et al. (2003)
Human	Primary cells	CBMC	Affymetrix gene array	Bradding et al. (2003)
TRPV3				
Not reported				
TRPV4				
Human	Cell line	HMC-1	WB, RT-PCR	Zhang et al. (2011)
Human	Cell line	HMC-1	RT-PCR	Kim et al. (2010)
Rat	Cell line	RBL-2H3	ICC	Yang et al. (2007)
Rat	Cell line	RBL-2H3	RT-PCR	Stokes et al. (2004)
TRPV5				
Not reported				

(Continued)

Table 2 | Continued

Species	Cell type	Name	Method	Reference
TRPV6				
Rat	Cell line	RBL-2H3	RT-PCR	Stokes et al. (2004)
TRPM1				
		Not reported		
TRPM2				
Human	Primary cells	HLMC	Affymetrix gene array	Bradding et al. (2003)
Human	Primary cells	CBMC	Affymetrix gene array	Bradding et al. (2003)
TRPM3				
		Not reported		
TRPM4				
Mouse	Primary cells	BMMC	RT-PCR, NB, WB, ICC	Vennekens et al. (2007)
TRPM5				
		Not reported		
TRPM6				
		Not reported		
TRPM7				
Rat	Cell line	RBL-2H3	RT-PCR	Stokes et al. (2004)
Human	Primary cells	HLMC	RT-PCR	Wykes et al. (2007)
Human	Cell line	HMC-1	RT-PCR	Wykes et al. (2007)
Human	Cell line	LAD-2 cells	RT-PCR	Wykes et al. (2007)
TRPM8				
Mouse	Primary cells	BMMC	RT-PCR	Medic et al. (2011)
Rat	Cell line	RBL-2H3	RT-PCR, ICC	Cho et al. (2010)
TRPA1				
Rat	Cell line	RBL-2H3	ICC, WB	Prasad et al. (2008)
TRPP1				
		Not reported		
TRPP2				
		Not reported		
TRPP3				
		Not reported		
TRPML1				
		Not reported		
TRPML2				
		Not reported		
TRPML3				
		Not reported		

BMMC, bone marrow-derived mast cells; CMBC, cord blood derived mast cells; HLMC, human lung mast cells; ICC, immunocytochemistry; IHC, immunohistochemistry; IP, Immunoprecipitation; NB, Northern blot; (q)RT-PCR, (quantitative) reverse transcriptase polymerase chain reaction; WB, Western blot.

family kinase Fyn expression of TRPC1 proteins was reduced by ∼30%, and cation currents, depolymerization of cortical F-actin and degranulation triggered by FcεRI-stimulation was significantly reduced whereas mast cell degranulation evoked by ATP, substance P, or thrombin was unaffected. Similar effects were observed by downregulation of TRPC1 expression using siRNAs against TRPC1 and the deficits in FcεRI-triggered mast cell activation could be rescued by exogenous expression of TRPC1 (Suzuki et al., 2010). *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 *Trpc4* and *Trpc5* (Suzuki et al., 2010) and TRPC4 proteins (Hernandez-Hansen et al., 2004) were found. TRPC5 transcript and protein expression was reported in RBL-2H3 cells (Ma et al., 2008). shRNA-mediated knock down of TRPC5 in RBL-2H3 cells was associated with a reduced Ca^{2+} entry following depletion of intracellular Ca^{2+} stores and based on overexpression experiments in these cells it was proposed that TRPC5 associates with Stim1 and Orai1 in a stoichiometric manner to build Ca^{2+} and Sr^{2+} permeable channels that can be discriminated from channels made by Orai1 and Stim1 (Ma et al., 2008). However, receptor-mediated Ca^{2+} entry or membrane currents have not been analysed in this study. *Trpc6* and *Trpc7* transcripts and proteins were also found in mouse BMMC (Hernandez-Hansen

et al., 2004; Sanchez-Miranda et al., 2010) and based on immunoprecipitation experiments using an antibody that was designed to detect all three members of the TRPC3/TRPC6/TRPC7 subfamily it was proposed that TRPC3/TRPC6/TRPC7, like TRPC1 (Suzuki et al., 2010), interact with fyn kinase during FcεRI-mediated mast cell activation (Sanchez-Miranda et al., 2010).

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 cation channels that are activated by a different range in temperatures, respectively, and by numerous 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 4α-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 physiological membrane potentials (Vennekens et al., 2000). Both proteins form constitutively active channels when heterologously expressed in different cell lines, but similar channel activity has never been recorded in the primary cell types that express TRPV5 or TRPV6, respectively. TRPV5 is essential for Ca^{2+} reabsorption in the kidney (Hoenderop et al., 2003a), and TRPV6 proteins determine Ca^{2+}-absorption in the epididymal epithelium and, thereby, sperm function and male fertility (Weissgerber et al., 2011).

All members of the TRPV proteins were reported to be expressed in various mast cell models except TRPV3 and TRPV5. For example, transcripts of *Trpv1*, *Trpv2*, *Trpv4*, and *Trpv6* were identified in RBL-2H3 cells (Stokes et al., 2004), *Trpv1*, *Trpv2*, and *Trpv6* in the human cell line HMC-1 (Zhang et al., 2011) and TRPV1 proteins in mast cells of the human bladder (Lazzeri et al., 2004) and skin (Stander et al., 2004). The TRPV1 specific agonists capsaicin or resiniferatoxin induced calcium uptake in several mouse mast cell lines, in BMMC, but not in PMC (Biro et al., 1998).

Treatment of BMMCs with ruthenium red, that is used as non-specific inhibitor of TRPV channels (Vriens et al., 2009), inhibited FcεeRI-mediated increase of cytosolic Ca^{2+} concentration (Lam et al., 2008). Mast cells are not only activated by specific allergens but also by various physical stimuli, e.g., rubbing, pressure, cold, heat which induce physical urticaria (Grabbe, 2001). These processes might be mediated through mechano- or thermosensitive TRP channels. Since ruthenium red inhibited the elevation of $[Ca^{2+}]_i$ and subsequent histamine release in RBL-2H3 cells induced by shear stress (Yang et al., 2009) and temperature increase (Stokes et al., 2004) or after irradiation with soft power lasers (Yang et al., 2007), a role of TRPV proteins was proposed in the above mast cell activating pathways. As Ruthenium Red inhibits several other channels in addition to TRPV channels, this concept requires validation by independent approaches.

Transcripts of *Trpv6* (formerly designated as Ca^{2+} transport protein 1, CaT1) have been detected in RBL-2H3 cells (Stokes et al., 2004). It had been proposed that TRPV6 comprises all or part of the CRAC pore (Yue et al., 2001) but later it was shown that TRPV6 expressed in HEK cells and CRAC in RBL-2H3 cells exhibit many differences in biophysical properties demonstrating that the pores of TRPV6 and CRAC are not identical (Voets et al., 2001). In this line, treatment of RBL-2H3 cells with antisense and siRNA probes directed against *Trpv6* transcripts, respectively, does not affect endogenous CRAC currents corroborating that TRPV6 is not a component of the native CRAC current in RBL mast cells. Nevertheless, expression of amino-terminal TRPV6 fragments, which are able to suppress currents through over-expressed TRPV6 channels, substantially suppressed activation of endogenous CRAC (Kahr et al., 2004).

TRPM CHANNELS

The members of the TRPM (melastatin) family are divided into four groups: TRPM1/3, TRPM2/8, TRPM4/5, and TRPM 6/7. For TRPM channels, heteromerization has only been reported for TRPM6 and TRPM7 so far (Chubanov et al., 2004, 2005; Li et al., 2006; Jiang, 2007). The Ca^{2+} permeability of channels formed by TRPM proteins ranges from monovalent selective (TRPM4 and TRPM5) to highly Ca^{2+} permeable (TRPM3α2, TRPM6, and TRPM7).

The founding member of this subfamily, *Trpm1* (initially termed melastatin), was initially identified as a gene that is downregulated 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 TRPM3α1 being poorly permeable for divalent cations, whereas TRPM3α2-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 μM) and activated by H_2O_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). *Trpm5*$^{-/-}$ mice show abolished sweet, umami, and bitter taste reception (Zhang et al., 2003) and impaired glucose-induced insulin secretion (Colsoul 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 preabsorbtion 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 BMMC's 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 *Trpm4*$^{-/-}$ 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). *Trpml1* 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 (Manzoni 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 from 0.1–0.5 to 2–3 μM which makes them accessible for patch-clamp measurements. In this way, it could be shown that expressed TRPML1 proteins form constitutively active cation channels which, besides Na^+ and Ca^{2+}, can conduct several other cations, e.g., Mn^{2+}, Zn^{2+}, and Fe^{2+} out of the lumen of the organelles into the cytosol. The mechanism leading to activation of TRPML1 is still unclear (Dong et al., 2008, 2010).

The TRPP (polycystin) family comprises eight members, from which only PKD2 (TRPP2, PC2, polycystin-2), PKD2-L1 (TRPP3, polycystin-L), and PKD2-L2 (TRPP5, polycystin-L2) are shown to be channels. TRPP2 is reported to form a Ca^{2+}-permeable cation channel in the plasma membrane that can be activated by downstream of G protein-coupled receptor and/or receptor-tyrosine kinase at the cell (Ma et al., 2005), but was also shown to form a Ca^{2+} release channel in the ER (Wegierski et al., 2009). TRPP3 is reported to form Ca^{2+}-permeable non-selective cation channels with a large single channel conductance modulated by pH (Chen et al., 1999; Huang et al., 2006). TRPP5 is thought to form a Ca^{2+}-permeable non-selective cation channel (Guo et al., 2000). As indicated above, individual members of TRP subfamilies are able to interact. However, TRPP2 was the first example showing that heteromultimerization cannot only occur between members of the same subfamily since interaction of TRPP2 was reported with TRPC1 (Tsiokas et al., 1999; Bai et al., 2008; Kobori et al., 2009; Zhang et al., 2009) or with TRPV4 (Kottgen et al., 2008; Stewart et al., 2010). Recently, also another example of interaction of TRP proteins of different subfamilies, i.e., TRPV4 with TRPC1, has been described (Ma et al., 2010). It has to be mentioned that the nomenclature of TRPP proteins was changed recently (Clapham et al., 2012), and TRPP2 is now designated TRPP1, TRPP3 is now TRPP2, and TRPP5 is now TRPP3. Until now, members of the TRPML- or TRPP-channel subfamily were not identified in mast cells.

MECHANISMS: HOW TRP CHANNELS REGULATE CHANGES IN $[Ca^{2+}]_i$ AND MAST CELL ACTIVATION

Taken together, TRP channels were found to influence cellular Ca^{2+} signaling by several mechanisms. First, by conducting Ca^{2+} ions to various degrees TRP channels directly contribute to 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 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 Na^+ entry and depolarization can enhance Ca^{2+} entry by gating of voltage-operated Ca^{2+} channels (Tsvilovskyy et al., 2009), they can do the opposite in non-excitable cells such as mast cells; here a significant part of stimulated Ca^{2+} entry enters the cell via inwardly rectifying CRAC channels, and TRP-mediated Na^+ entry and subsequent depolarization reduces the driving force for Ca^{2+} entry by shifting the membrane potential toward more positive potentials (Vennekens et al., 2007). A counteracting mechanism by a Ca^{2+} activated K^+ channel leading to membrane hyperpolarization and an increase of the driving force for Ca^{2+} entry following FcεRI-stimulation was shown for SK4 ($K_{Ca}3.1$) proteins (Shumilina et al., 2008) emphasizing the relevance of this regulatory principle for adjusting $[Ca^{2+}]_i$ and activation of mast cells. Third, TRP channels can be activated or inhibited by themselves by Ca^{2+} which further contributes to the complexity of regulation of $[Ca^{2+}]_i$. TRP channels that are activated by Ca^{2+} include TRPC1, TRPC4, TRPC5, TRPC6, TRPV4, TRPM2, TRPA1, TRPM4, and TRPM5. Also many TRP channels are modulated by Ca^{2+} via complex signaling cascades including Ca^{2+}/calmodulin binding, Ca^{2+}-dependent modulation of phospholipase C, and Ca^{2+}-dependent activation of PKC. Fourth, there is emerging evidence that several TRP channels are also located in the membrane of the sarco/endoplasmic reticulum (SR/ER), endosomes, lysosomes, or other intracellular vesicles where they can serve as Ca^{2+} release channels and conduct 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 Ca^{2+}-conducting channels in the SR/ER, and TRPML1, TRPM2, and TRPV2 may function as 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 Ca^{2+}-dependent mast cell functions analysed measurements of global cytoplasmic Ca^{2+} concentration rather than the nature of the Ca^{2+} signals, e.g., differences in the frequency of transient episodic Ca^{2+} elevations (Ca^{2+} spikes/oscillations) and subcellular localization and direction of Ca^{2+} signals such as Ca^{2+} waves which may be crucial for distinct mast cell functions. In this line, a threshold of 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 Ca^{2+} entry pathway might be achieved by spatially sequestered calmodulin molecules as mediators. Likewise, it would not be surprising if also a specific localization pattern of certain TRP channel proteins and their dynamic change during mast cell activation could be identified in the future as a mechanism that explains a specific pattern of mast cell activation such as activation of individual transcription factors or release of a defined set of mast cell mediators.

ACKNOWLEDGMENTS

This work was supported by the Deutsche Forschungsgemeinschaft including the Schwerpunktprogramm 1394 ("Mast cells – promotors of health and modulators of disease," SPP 1394).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 14 March 2012; accepted: 22 May 2012; published online: 12 June 2012.

Citation: Freichel M, Almering J and Tsvilovskyy V (2012) The role of TRP proteins in mast cells. Front. Immun. ***3****:150. doi: 10.3389/fimmu.2012.00150*

This article was submitted to Frontiers in Molecular Innate Immunity, a specialty of Frontiers in Immunology.