

The Role of Transient Receptor Potential Cation Channels in Ca²⁺ Signaling

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The 28 mammalian members of the super-family of transient receptor potential (TRP) channels are cation channels, mostly permeable to both monovalent and divalent cations, and can be subdivided into six main subfamilies: the TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), and the TRPA (ankyrin) groups. TRP channels are widely expressed in a large number of different tissues and cell types, and their biological roles appear to be equally diverse. In general, considered as polymodal cell sensors, they play a much more diverse role than anticipated. Functionally, TRP channels, when activated, cause cell depolarization, which may trigger a plethora of voltage-dependent ion channels. Upon stimulation, Ca²⁺ permeable TRP channels generate changes in the intracellular Ca²⁺ concentration, [Ca²⁺]_i, by Ca²⁺ entry via the plasma membrane. However, more and more evidence is arising that TRP channels are also located in intracellular organelles and serve as intracellular Ca²⁺ release channels. This review focuses on three major tasks of TRP channels: (1) the function of TRP channels as Ca²⁺ entry channels; (2) the electrogenic actions of TRPs; and (3) TRPs as Ca²⁺ release channels in intracellular organelles.

Transient receptor potential (TRP) channels constitute a large and functionally versatile family of cation-conducting channel proteins, which have been mainly considered as polymodal unique cell sensors. The first TRP channel gene was discovered in *Drosophila melanogaster* (Montell and Rubin 1989) in the analysis of a mutant fly whose photoreceptors failed to retain a sustained response to maintained light stimuli. So far, more than 50 TRP channels have been identified with representative members in many species. The evolutionary first TRP channels in protists, chlorophyte algae,

choanoflagellates, yeast, and fungi are primary chemo-, thermo-, or mechanosensors (Cai 2008; Wheeler and Brownlee 2008; Chang et al. 2010; Matsuura et al. 2009). Many of these functions are remarkably conserved from protists, worms, and flies to humans (Montell 2005; Pedersen et al. 2005; Nilius et al. 2007; Damann et al. 2008). More than 50 *trp* genes have been cloned so far that comprise approximately 20% of the known genes encoding ion channels. In mammals, 28 TRP channels were found and classified according to homology into 6 subfamilies: TRPC (canonical), TRPV (vanilloid),

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TRPM (melastatin), TRPA (ankyrin), TRPML (mucolipin), and TRPP (polycystin) (Fig. 1). TRPs are expressed in numerous excitable and nonexcitable tissues, if not in all cell types. They are involved in manifold physiological functions, ranging from pure sensory functions, such as pheromone signaling, taste transduction, nociception, and temperature sensation, over homeostatic functions, such as Ca^{2+} and Mg^{2+} reabsorption and osmoregulation, to many other motile functions, such as muscle contraction and vaso-motor control. We are still at the very beginning of identifying all the diverse physiological functions of this intriguing ion channel family, and our knowledge about TRP channel expression and functioning in various tissues of mammals is limited. Accumulating evidence, however, suggests that TRP channels play prominent roles in the regulation of the intracellular calcium level in both excitable and nonexcitable cells.

The molecular architecture of TRP channels is reminiscent of voltage-gated channels and comprises six putative transmembrane segments (S1–S6), intracellular N- and C-termini, and a pore-forming reentrant loop between S5 and S6 (Gaudet 2008b). The length of the cytosolic tails varies greatly between TRP channel subfamilies, as do their structural and functional domains (for detailed reviews see Owsianik et al. 2006a). The TRPC and TRPM family members all contain a 25-amino-acid motif (the TRP domain) containing a TRP box C-terminal to S6, but this domain is not present in the other families. Although TRPC and TRPV family members contain 3–4 ankyrin repeats in their N-terminal cytoplasmic tail, TRPA1 contains 14 ankyrin repeats, and they are not present in the other families. Lastly, TRPC and TRPM family members contain protein-rich sequences in the region C-terminal of the TRP domain (known as the TRP box 2).

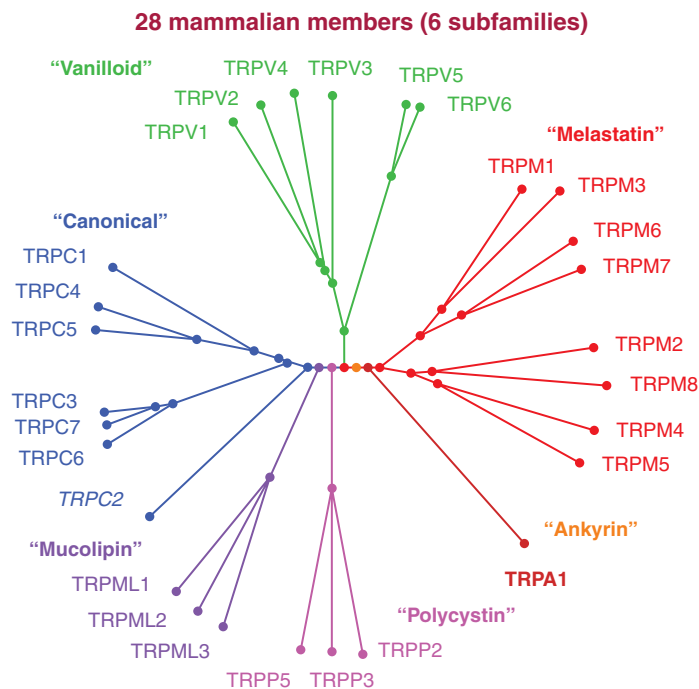


Figure 1. Phylogenetic tree of the mammalian TRP-channel superfamily. TRPC (canonical), TRPM (melastatin), TRPV (vanilloid), TRPA (ankyrin), TRPP (polycystin), and TRPML (mucolipin) are the only identified subfamilies in mammals.



The TRP box is most likely important for binding of phosphatidylinositol phosphates, such as PI(4,5)P₂ (Rohacs 2007). So far, our knowledge of the three-dimensional structure is limited, as only parts of TRP proteins have been crystallized. Most of the TRP channels probably form tetramers, in which the capacity to function as homo- or heteromers is still a matter of debate. However, increasing evidence suggests heteromultimeric channel assembly within one subfamily, creating a variety of different channels with unique properties, as compared to homomers (Strubing et al. 2001; Smith et al. 2002). Topics to be explored further include the association with accessory proteins (e.g., beta subunits) and the forming of signalplexes (Montell 2003; Peng et al. 2007; Redondo et al. 2008), the various mechanisms of insertion and retrieval in and from the plasma membrane, and the general processes for the regulation of mainly intracellular location or their trafficking to the plasma membrane.

Importantly, most, if not all, TRP channels are modulated by Ca²⁺ itself, which generates positive or negative feedback loops. Thus, regarding the modulation of Ca²⁺ signaling, TRP channels provide a huge plasticity to the overall control of the intracellular Ca²⁺ concentration [Ca²⁺]_i.

This review focuses on the functional role of TRP channels as modulators of intracellular Ca²⁺ signaling. Changes in the concentration of free cytosolic Ca²⁺ ([Ca²⁺]_i) are of fundamental importance in different stages of the cell cycle, starting from the fertilization and embryonic pattern formation, to cell differentiation and proliferation, and cell death. Furthermore, [Ca²⁺]_i plays a role in different cellular processes including transmitter release, muscle contraction, and gene transcription (Berridge et al. 2000). TRP channels can contribute to changes in [Ca²⁺]_i, either by acting as Ca²⁺-entry pathways in the plasma membrane or by changing the membrane polarization; in this way modulating the driving force for Ca²⁺ entry mediated by alternative pathways. Alternatively, [Ca²⁺]_i can be elevated by the release from intracellular stores (Bootman et al. 2001). In addition, TRP channels are functionally

linked with voltage-dependent Ca²⁺-entry channels that are activated by depolarization, for example, due to TRP gating. By changing the membrane potential and local Ca²⁺ gradients, TRP channels contribute to modulating the driving force for Ca²⁺ entry and provide intracellular pathways for Ca²⁺ release from cellular organelles.

For more detailed information on TRP channels regarding structure, gating, and special functional aspects, we refer a wealth of excellent reviews (Desai and Clapham 2005; Montell 2005; Ramsey et al. 2006; Nilius et al. 2007; Vennekens et al. 2008; Latorre et al. 2009; Vriens et al. 2009). For more detailed information, we direct the interested reader to databases such as <http://www.ensembl.org/index.html> and <http://www.iuphar-db.org/DATABASE/FamilyMenuForward?familyId=78> (see also Clapham et al. 2009).

TRPs AS Ca²⁺ ENTRY CHANNELS

Ca²⁺ Permeable TRP Pores

Although most TRPs are Ca²⁺ permeable, the selectivity varies greatly between the different members with P_{Ca}/P_{Na} ratios ranging from <1 for TRPM1 to >100 for TRPV5 and TRPV6 (Fig. 2). This variance reflects different pore structures and obviously also differences in the dynamic pore behavior; for example, pore dilation by activations with various agonists (Chung et al. 2008; Karashima et al. 2010). In general, there is no high homology in the primary structure of the putative selectivity filter regions throughout all TRP subfamilies (Owsianik et al. 2006b). For TRPV5 and TRPV6, it is shown that the Ca²⁺-permeability depends on D⁵⁴² in TRPV5 and the corresponding D⁵⁴¹ in TRPV6 (Nilius et al. 2001). As TRPV5 and TRPV6 form homo- and heteromultimers, it appears that the Ca²⁺ selectivity in these channels depends on a ring of four aspartate residues in the pore of the channel, corresponding to the ring of four negatively-charged residues (aspartates and/or glutamates) in the pore of voltage-gated Ca²⁺ channels (Ellinor et al. 1995; Hoenderop et al. 2003). It is shown that neutralization of the D⁵⁴⁶ in

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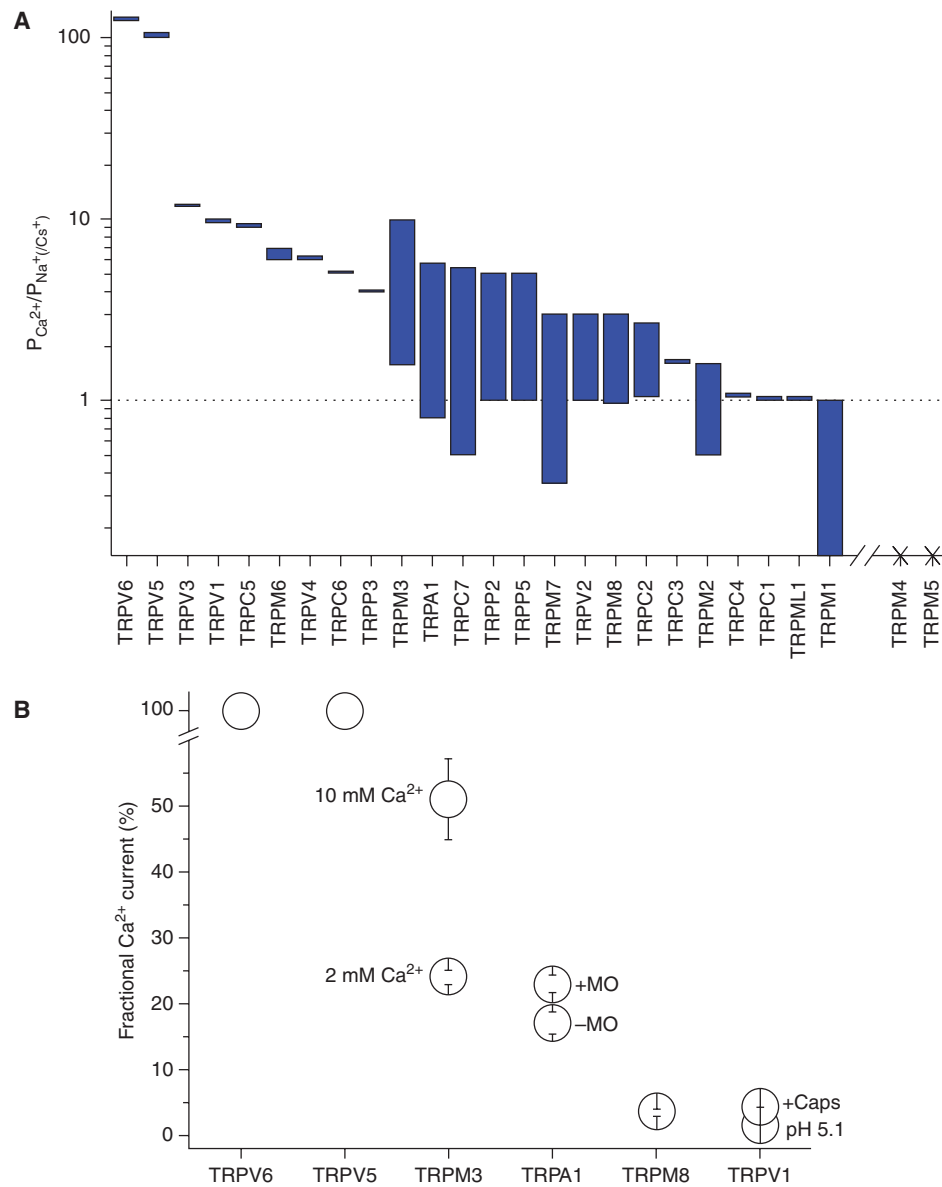


Figure 2. Ca^{2+} selectivity of TRP channels. (A) Ca^{2+} selectivity of TRP channels expressed as $P_{Ca^{2+}}/P_{Na^{+}/Cs^{+}}$ (depending on availability). Bars indicate maximal and minimal values found in literature; TRPM4 and TRPM5 are impermeable to Ca^{2+} (for TRPM1, values are deduced from Oancea et al. 2009). (B) Fractional Ca^{2+} current of TRP channels as found in literature (for TRPM3 Oberwinkler personal communication, see Drews et al. 2010).

TRPV1 and the corresponding D^{682} in TRPV4 also reduce the Ca^{2+} permeability. For TRPV4, additional neutralization of D^{672} reduces the divalent selectivity even further, while introducing a negative charge, instead of M^{680} abolishing the Ca^{2+} permeability completely

(Garcia-Martinez et al. 2000; Voets et al. 2002). More recently, it is shown that also in the *Drosophila* TRP an aspartate (D^{621}) plays an important role in determining the Ca^{2+} permeability (Liu et al. 2007a), whereas neutralization of the negative charges in the loops between TM5 and



TM6 of TRPC5 (E⁵⁴³, E⁵⁹⁵, E⁵⁹⁸) and TRPC1 (all seven, D to N and E to Q) resulted in a decreased La²⁺ and Ca²⁺ permeability (Jung et al. 2003; Liu et al. 2003). This suggests that the negatively-charged residues determining the pore properties of TRPC1 and TRPC5 are located in the distal parts of the putative pore entrance. A pore study of TRPM4, which is impermeable to Ca²⁺, showed that substitution of residues E⁹⁸¹ to A⁹⁸⁶ with the selectivity filter of TRPV6 yielded a functional channel with the gating hallmarks of TRPM4 (activation by Ca²⁺, voltage dependence) and with a TRPV6-like sensitivity to block by extracellular Ca²⁺, Mg²⁺, and Ca²⁺ permeation (Nilius et al. 2005a). Two recent studies showed that E¹⁰²⁴ and D¹⁰³¹ play an important role in the Ca²⁺ permeation through TRPM6, and that restoration of only two residues in the human TRPM2 (Q981E/P983Y) to the evolutionary, more ancient Nudix-linked channel residues, significantly increased the Ca²⁺ permeability, whereas introducing the newer sequence in TRPM7 (E1047Q/Y1049P) resulted in the loss of Ca²⁺ permeability (Topala et al. 2007; Mederos y Schnitzler et al. 2008). Another study showed that neutralizing the charges of residues E¹⁰⁵² and E¹⁰⁴⁷ of TRPM7 and the corresponding residues in TRPM6 (E¹⁰²⁴ and E¹⁰²⁹) reduced the Ca²⁺ permeation (Li et al. 2007).

Although pore structures have been considered as relatively stable, evidence is accumulating that for some TRP channels the pore diameter and also Ca²⁺ permeation depend on the mode of activation; for example, the activating agonist. Such dynamic pore behavior was first observed for P2X channels (Egan and Khakh 2004). Activation of TRPV1 leads to time-dependent and agonist-concentration-dependent increases in relative permeability to large cations and changes in Ca²⁺ permeability that parallels a pore dilation. TRPV1 agonists showed different capabilities for evoking ionic selectivity changes. Very likely, for TRPV1, protein kinase C-dependent phosphorylation of S⁸⁰⁰ in the TRPV1 C-terminus increases agonist-evoked ionic selectivity changes. Thus, the qualitative signaling properties of TRPV1 are dynamically modulated during channel

activation, a process that probably shapes TRPV1 (Chung et al. 2008). A similar situation holds for TRPA1. From the relative permeability of the nonstimulated TRPA1 channel to cations of different sizes, a diameter of ~11 Å is calculated for the channel pore, which fits with the pore size of TRPM6, TRPV1, and TRPP2, but is significantly larger for the highly Ca²⁺ permeable channels TRPV5 and TRPV6 (~7.5 Å and 5.4 Å). Under conditions of activation by electrophilic compounds such as AITC (allyl isothiocyanate, or mustard oil, MO), the TRPA1 channel undergoes a pore dilation by ~3 Å. This dynamic pore behavior was coupled with an increased Ca²⁺ permeation and an increased fraction of Ca²⁺ contributing to the total current. Upon MO stimulation, P_{Ca}/P_{Na} changed from ~5.7 to 7.9, and the fractional Ca²⁺ current from 17.0% to 23.3%. This pore dilation is probably not present for nonelectrophilic agonists and also disappeared when a negatively-charged residue in the pore, D⁹¹⁸, was changed to noncharged residues. Again, this negative charge in the TRPA1 pore determines the Ca²⁺ entry (Chen et al. 2009; Karashima et al. 2010). Also, for TRPV5, a pH-dependent pore dilation has been described (Yeh et al. 2005). This dynamic pore behavior adds a new regulation mechanism to agonist-induced Ca²⁺ entry. Pore dilation, modulation of the fractional Ca²⁺ current, and changes of the Ca²⁺ permeation are modulator properties for Ca²⁺ signaling in likely many TRP channels.

Thus, depending on the pore structure, TRP channels vary in their pore size and in the permeation for Ca²⁺, which is indicated by the P_{Ca}/P_{Na} (or P_{Cs}) ratios. Obviously, the Ca²⁺ permeation also varies under different experimental conditions, might be influenced by associated proteins, and even shows a dynamic behavior for some TRP channels. Figure 2 gives an overview of Ca²⁺ permeation properties and their variability.

TRPCs

The mammalian members of the TRPC family can be divided into 4 subfamilies on the basis of functional similarities and sequence

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alignment: TRPC1, TRPC2, TRPC3/6/7, and TRPC4/5. TRPC channels in general are non-selective Ca^{2+} permeable cation channels, but the selectivity ratio $P_{\text{Ca}}/P_{\text{Na}}$ varies significantly between the different family members (see Fig. 2). With a few exceptions, expression of TRPC family members is broad; thus, generally, most cell types contain multiple TRPCs (for examples, see Montell et al. 2002; Montell 2005). The characterization is further complicated by different heterotetramers. It is shown that TRPC1 can form heteromers with TRPC4 and 5, and the TRPC subfamilies TRPC4/5, and TRPC3/6/7 can form heteromers among themselves, with properties that can differ significantly from those of the homotetramers (Strubing et al. 2001; Goel et al. 2002; Hofmann et al. 2002; Strubing et al. 2003; Schilling and Goel 2004). Activation of TRPC channels occurs mainly via different isoforms of phospholipase C (PLC) (Venkatachalam et al. 2002).

The relation between the constituents, STIM1 and ORAI1, of the best characterized store-operated Ca^{2+} channel (SOC) carrying I_{CRAC} and the contribution of TRPC channels is still a matter of dispute. It was first shown that TRPC1/STIM1 and ORAI1 very likely form ternary complexes to contribute to a SOC channel (Ambudkar et al. 2007). ORAI1 proteins may interact with TRPCs and act as regulatory subunits that confer STIM1-mediated store depletion sensitivity to these channels (Lu et al. 2010; Liao et al. 2007). STIM1 has been shown to bind to TRPC1, TRPC4, and TRPC5 and is therefore involved in store-operated Ca^{2+} entry (SOCE) (Yuan et al. 2007; Sours-Brothers et al. 2009). The involvement of TRPC channels in SOCE may depend on special membrane structures, such as lipid rafts (Pani et al. 2008). In general, a majority of reports described TRPC1 as a store-operated channel whose gating mechanism is still to be elucidated (Worley et al. 2007; Kim et al. 2009c; Ng et al. 2009). So far, as concluded from a plethora of experimental evidence, TRPC channels might, under certain circumstances, act as SOCs, but are to be clearly distinguished from the calcium-release-activated calcium channels, as they show distinct properties: high Ca^{2+}

selectivity; very small single channel conductance; distinct Ca^{2+} dependent modulation, e.g., fast and slow inactivation; and slow decay in divalent free solutions (for reviews and more detailed descriptions, see Vaca 2010; Bolotina 2008; Birnbaumer 2009; Kiselyov and Patterson 2009; Yuan et al. 2009).

TRPC1 (ENSG00000144935; TRPC1) is activated by the neuronal metabotropic glutamate receptor mGluR1 and thus contributes to the slow excitatory postsynaptic potential (EPSP) (Kim et al. 2003). Furthermore, TRPC1 provides an important route for Ca^{2+} entry after agonist, growth factor, and PKC induction in different cell types such as endothelial cells (Kamouchi et al. 1999; Nilius and Droogmans 2001; Tiruppathi et al. 2006), platelets (Authi 2007), smooth muscle cells (Dietrich et al. 2006), and B-lymphocytes (Mori et al. 2002). One report identifies TRPC1 as the mechanosensitive cation channel, responsible for transducing membrane stretch in cationic currents (Maroto et al. 2005), but this is disputed (Gottlieb et al. 2008). In *Trpc1* KO mice, it is shown that the salivary gland fluid secretion regulated by neurotransmitters is severely reduced (Liu et al. 2007b). TRPC1 is also activated by orexin A, a peptide hormone associated to the regulation of sleep/wakefulness states, alertness, and appetite (Larsson et al. 2005). More recently, it is shown that knock-down of *Trpc1* in zebrafish impaired angiogenesis, an effect that could be rescued by reintroducing TRPC1, which is reminiscent of the role of TRPCs in axon guidance (Yu et al. 2010).

Trpc2 (ENSMUSG00000058020; TRPC2) in humans is a pseudogene (Yildirim and Birnbaumer 2007), but in rodents it plays an important role in pheromone detection via the vomeronasal sensory neurons (VSN) (Yildirim and Birnbaumer 2007). TRPC2 is also shown to be important for the Ca^{2+} signaling in spermatozoa after egg ZP3 stimulation (Yildirim and Birnbaumer 2007). Lastly, TRPC2 is shown to be involved in Ca^{2+} release from the intracellular stores (Gailly and Colson-Van Schoor 2001; Tong et al. 2004; Yildirim and Birnbaumer 2007).



Expression of TRPC3 (ENSG00000138741; TRPC3) is highest in brain, smooth, and cardiac muscle cells (Ricchio et al. 2002b; Clapham 2003). TRPC3 is a constitutively active receptor-operated channel that can be further stimulated by DAG (Lemonnier et al. 2008). As all TRPCs, TRPC3 can interact directly via a CIRB region with both IP₃R and Calmodulin (CaM). TRPC3 channel activation by IP₃ can lead to the constriction of cerebral arteries (Wedel et al. 2003; Xi et al. 2008) and is involved in synaptogenesis and growth-cone guidance (Amaral and Pozzo-Miller 2007b). The *Trpc3* gene was found to be damaged in human T-cell mutants defective in Ca²⁺ influx; introduction of the complete human *TRPC3* cDNA into those mutants rescued the Ca²⁺ currents, as well as TCR-dependent Ca²⁺ signals (Philipp et al. 2003). TRPC3 activation by purinergic receptors results in both Ca²⁺ influx and depolarization of endothelial cells and vasoconstriction in smooth muscle cells (Ahmed and Malik 2005; Kwan et al. 2007).

Expression of TRPC4 (ENSG00000100991; TRPC4) is found in endothelium and smooth muscle cells (Beech 2005; Tiruppathi et al. 2006), intestinal pacemaker cells (ICC) (Kim et al. 2006), in many brain regions (Zechel et al. 2007), adrenal glands (Philipp et al. 2000), and in kidneys (Freichel et al. 2005). It is suggested that TRPC4 is an essential component of the nonselective cation channel involved in neuromodulation of stomach smooth muscle after muscarinic stimulation (Lee et al. 2005). Furthermore, a reduced agonist-induced Ca²⁺ entry and vasorelaxation is shown in the vascular endothelium of TRPC4-deficient mice (Freichel et al. 2001).

Similar to TRPC4, TRPC5 (ENSG00000072315; TRPC5) is expressed in multiple tissues, including brain tissue (Hofmann et al. 2000). In the CNS, it is shown that TRPC5 can form heteromeric cation channels with TRPC1, and these heteromultimers may play an important role during brain development (Strubing et al. 2001; Strubing et al. 2003). In neurons, TRPC5 is loaded to vesicular packages for neuronal transport via association with synaptotagmin and stathmin-2 (Greka et al. 2003).

TRPC5 shows a striking voltage dependence, shifting between outwardly rectifying and doubly rectifying shapes (called phases) depending on the time in the activation-deactivation cycle. These phase transitions can be modulated by external factors such as La³⁺ and the scaffolding protein EBP50 (Obukhov and Nowycky 2004; Obukhov and Nowycky 2008). Vesicular insertion of TRPC5 from a subplasmalemmal reserve pool is shown to be regulated by EGF-RTK, in a manner depending on PI3K, Rac, and phosphatidylinositol 4-phosphate 5-kinase (PIP(5)K) (Bezzarides et al. 2004). This process is shown to be important for the regulation of hippocampal neurite length and growth-cone morphology (Bezzarides et al. 2004). Noticeably, TRPC5 is required for muscarinic persistent responses involved in establishing a transient working memory in the entorhinal cortex (Zhang et al. 2010). More recently, it was shown that TRPC5 is important for amygdala function and fear-related behavior (Ricchio et al. 2009). TRPC5 is also activated by nitric oxide (NO), which was shown to be achieved by nitrosylation of residues C⁵⁵³ and C⁵⁵⁸ (Yoshida et al. 2006).

TRPC6 (ENSG00000137672; TRPC6) and TRPC7 (ENSG00000069018; TRPC7) are closely related, but whereas expression of TRPC6 is highest in the lung and brain, TRPC7 is mainly expressed in the kidney and pituitary gland (Hofmann et al. 2000; Ricchio et al. 2002a; Montell 2005). It is shown that thrombin activation of TRPC6 can induce Ca²⁺ entry in platelets (Hassock et al. 2002). The channel is also shown to be an important part of the vascular α_1 -activated Ca²⁺-permeable cation channel in smooth muscle (Inoue et al. 2001; Jung et al. 2002). Furthermore, *Trpc6* KO mice showed an elevated blood pressure and increased vascular smooth muscle contractility that was only partly recovered by the constitutively-active TRPC3-type channels, which are up-regulated in the smooth muscle cells of *Trpc6* KO mice (Dietrich et al. 2005). Lastly, TRPC6 channel activity at the slit diaphragm is shown to be essential for proper regulation of podocyte structure and function (Reiser et al. 2005; Graham et al. 2007). The functional

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role of TRPC7 is still unclear, but it is suggested that TRPC7 conducts Ca^{2+} in AT1-induced myocardial apoptosis via a calcineurin-dependent pathway and can thereby contribute to the process of heart failure (Satoh et al. 2007).

TRPVs

Similar to the TRPC family, the TRPV (vanilloid) family can be divided into four subfamilies on the basis of structure and function, namely TRPV1/TRPV2, TRPV3, TRPV4, and TRPV5/6 (Vennekens et al. 2008). As mentioned above, TRPV5 and 6 are the only highly Ca^{2+} -selective channels in the TRP channel family (Nilius et al. 2000; Vennekens et al. 2000; Nilius et al. 2001), whereas TRPV1–4 are nonselective cation channels (permeability ratio $P_{\text{Ca}}/P_{\text{Na}}$ between ~ 1 and ~ 15 ; see Fig. 2) that are activated by temperature and by numerous other stimuli (Nilius et al. 2003; Nilius et al. 2004; Vennekens et al. 2008; Vriens et al. 2009). All channels of the TRPV family contain 3–6 NH_2 -terminal ankyrin repeats (for details, see Gaudet 2008a; Gaudet 2008b; Gaudet 2009).

TRPV1 (ENSG00000196689; TRPV1) was the first mammalian TRPV family member to be discovered and has been studied most extensively. Expression of TRPV1 was first identified in the pain-sensitive neurons of the dorsal root ganglion (DRG) and trigeminal ganglion (TG) neurons, but is also present in the terminals of spinal and peripheral nerves. TRPV1 expression is also shown in multiple non-neuronal cell types (Hayes et al. 2000). Activation of TRPV1 is voltage-dependent and can be induced by capsaicin and temperature ($>42^\circ\text{C}$) (Voets et al. 2004a). *Trpv1* KO mice showed the importance of the channel in the detection and integration of different painful chemical and thermal stimuli (Caterina et al. 1997). In the pancreas, it is shown that TRPV1 is involved in the release of substance P (Nathan et al. 2001). In the bladder, TRPV1 is an important target for the treatment of cystitis-induced bladder overactivity, but the exact localization is still under debate (De Ridder and Baert 2000; Charrua et al. 2007; Wang et al. 2008; Everaerts et al. 2009).

TRPV2 (ENSG00000187688; TRPV2) has 50% sequence identity to TRPV1 and is also expressed in DRG neurons, different brain regions, and non-neuronal tissues, including GI tract and smooth muscle cells (Vennekens et al. 2008). Similar to TRPV1, TRPV2 is also activated by heat but only at higher, noxious temperatures ($>52^\circ\text{C}$) compared to TRPV1 (Caterina et al. 1999). Growth factors, such as insulin-like growth factor (IGF-1), can activate TRPV2 by vesicular insertion in the membrane, a process that can be associated to myocyte degeneration caused by the disruption of dystrophin-glycoprotein complexes (Kanzaki et al. 1999; Iwata et al. 2003). Furthermore, in a dystrophin-deficient (*mdx*) mouse, a model for muscular dystrophy, it was shown that expression of a dominant-negative TRPV2 reduced the muscle damage (Iwata et al. 2009). TRPV2 has also been described as a mechano-sensor in vascular smooth muscle cells, as it can function as a stretch-activated channel (Muraki et al. 2003; Beech et al. 2004). More recently, it is shown that TRPV2 is of fundamental importance in innate immunity, as early phagocytosis was impaired in macrophages lacking the cation channel (Link et al. 2010).

TRPV3 (ENSG00000167723; TRPV3) is expressed in DRG and TG neurons, the brain, the tongue, and the testis (Smith et al. 2002; Xu et al. 2002; Chung et al. 2003; Chung et al. 2005). Expression is also high in the skin, keratinocytes, and in the cells surrounding hair follicles (Peier et al. 2002b; Gopinath et al. 2005; Moqrich et al. 2005; Asakawa et al. 2006; Xu et al. 2006; Mandadi et al. 2009). TRPV3 is activated by innocuous warm temperatures (>30 – 33°C), and the natural compounds camphor, thymol carvacrol, and eugenol, which are also potent sensitizers for temperature activation of the channel (Peier et al. 2002b; Xu et al. 2002; Moqrich et al. 2005; Xu et al. 2006). The importance of TRPV3 as a temperature sensor is shown in *Trpv3* KO mice, in which the responses to innocuous and noxious heat are dramatically diminished, whereas responses to other sensory modalities remained unaltered (Moqrich et al. 2005). More recently, it is shown that heating of keratinocytes causes

release of ATP that can consequently activate termini of neighboring DRG neurons, a process that is compromised in keratinocytes from TRPV3-deficient mice (Mandadi et al. 2009). TRPV3 is required for forming the skin-barrier function and keratinocytes cornification and forms a signalplex with TGF- α /EGFR (Cheng et al. 2010a).

TRPV4 (ENSG00000111199; TRPV4) is a channel that is widely expressed in the brain, DRG neurons, and multiple non-neuronal tissues including bone, chondrocytes, insulin-secreting β -cells, keratinocytes, smooth muscle cells, hair cells of the inner ear, and different epithelial cell types (Vennekens et al. 2008; Everaerts et al. 2010). TRPV4 can be activated by moderate temperatures ($>24^{\circ}\text{C}$) and is, as such, constitutively active at normal body temperatures. Other activating stimuli include shear stress, cell swelling, anandamide, arachidonic acid, and 4 α -phorbol 12,13-didecaneate (4 α -PDD) (Watanabe et al. 2002a; Watanabe et al. 2002b; Nilius et al. 2003; Watanabe et al. 2003; Nilius et al. 2004). It is reported that TRPV4 plays a role in thermoregulation via epidermal keratinocytes (Chung et al. 2003; Chung et al. 2004). As a mechanical and osmotic stimulus-induced nociceptor, TRPV4 seems important in DRGs and TGs (Alessandri-Haber et al. 2003; Liedtke and Friedman 2003; Suzuki et al. 2003). Lastly, it is shown that TRPV4 expressed in osteoblasts and osteoclasts may play a role in bone formation and remodelling (Masuyama et al. 2008; Mizoguchi et al. 2008) whereas in chondrocytes, it is shown to regulate the Sox9 pathway involved in the regulation of chondrocyte polarity and differentiation and in endochondral ossification (Muramatsu et al. 2007).

TRPV5 (ENSG00000127412; TRPV5) and TRPV6 (ENSG00000165125; TRPV6) are close homologs and the only members of the TRP family that are highly Ca²⁺-selective. TRPV5 and TRPV6 can function as homomers, but TRPV5/6 heterotetramers are also formed (Hoenderop et al. 2003). Both channels are constitutively active and are essential for Ca²⁺ reabsorption in the kidney (TRPV5) and in the intestine (TRPV6) (den Dekker et al. 2003;

Nijenhuis et al. 2003a; Nijenhuis et al. 2003b). Both channels are tightly regulated by extracellular and intracellular Ca²⁺ concentrations, although their kinetics differ (Voets et al. 2001; Nilius et al. 2002; Voets et al. 2003; Hoenderop et al. 2005). The striking Ca²⁺-dependent inactivation probably reflects a Ca²⁺-induced PI(4,5)P₂ depletion (Thyagarajan et al. 2008; Thyagarajan et al. 2009).

TRPMs

The members of the TRPM (melastatin) family are divided into 4 groups on the basis of sequence homology: TRPM1/3, TRPM2/8, TRPM4/5, and TRPM 6/7. Ca²⁺ permeability in the TRPM family ranges from impermeable to Ca²⁺ (TRPM4 and 5) to highly Ca²⁺ permeable (TRPM3, 6 and 7; see Fig. 2). Unlike the previously-discussed TRP channels, TRPM channels lack the N-terminal ankyrin repeats.

Lower expression levels of TRPM1 (ENSG00000134160; TRPM1) in malignant melanoma cell lines suggested that TRPM1 had a tumor suppressor function, but this was debated in further research (Duncan et al. 1998; Duncan et al. 2001; Miller et al. 2004). It is thought that TRPM1 is a constitutively open, nonselective cation channel, but little is known about the functional properties and cellular functions of this channel, partly because of the huge number of different splice variants. More recently, it was shown that a TRPM1 long-form (TRPM1-L) plays an important role in the ON pathway of retinal bipolar cells, and this might explain the complete congenital stationary night blindness seen in patients with mutations in *Trpm1* (Koike et al. 2010; Audo et al. 2009; Li et al. 2009; Shen et al. 2009; van Genderen et al. 2009).

TRPM2 (ENSG00000142185; TRPM2) is a chanzyme, forming a nonselective cation channel fused C-terminally to an enzymatic ADP-ribose pyrophosphatase domain (Perraud et al. 2001; Perraud et al. 2003). Expression of TRPM2 is found highest in the brain, but is also found in different peripheral cell types (Kraft and Harteneck 2005).

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It is shown that activation of TRPM2 causes predisposition to apoptosis and cell death and that inhibition of TRPM2 is neuroprotective, probably because TRPM2 is activated by H₂O₂ and functions as a sensor for the cellular redox status (Kuhn et al. 2005; McNulty and Fonfria 2005; Zhang et al. 2006). This activation is prevented by a truncated TRPM2 isoform (TRPM2-S), generated by alternative splicing of the full-length protein (TRPM2-L) (Zhang et al. 2003a).

Transcription of TRPM3 (ENSG000000-83067; *TRPM3*), similar to TRPM1, results in a number of different mRNA species, and this variability is further enhanced by the presence of different starting positions and C-terminal ends (Grimm et al. 2003; Lee et al. 2003). Expression of TRPM3 has been shown in the human brain and kidney, although it was undetectable in a mouse kidney (Grimm et al. 2003; Lee et al. 2003). TRPM3 forms a channel permeable to divalent cations and is activated by D-erythro-sphingosine, pregnenolone sulfate, activation of an endogenous muscarinic receptor, and by a decreased extracellular osmolarity. This activation by hypotonicity argues for a role for TRPM3 in the renal osmo-homeostasis (Grimm et al. 2003; Lee et al. 2003; Grimm et al. 2005).

TRPM4 (ENSG00000130529; *TRPM4*) and TRPM5 (ENSG00000070985; *TRPM5*) are two closely-related cation channels that are ubiquitously expressed; whereas TRPM4 expression is highest in the heart, pancreas, and placenta, TRPM5 expression is found mainly in the intestine, taste buds, and pancreas but also in the stomach, lung, testis, and brain (Ullrich et al. 2005; Fonfria et al. 2006; Zhang et al. 2003b; Kokrashvili et al. 2009; Colsoul et al. 2010). As these channels are impermeable to Ca²⁺, they do not function as Ca²⁺-entry channels. They do, however, play a role in [Ca²⁺]_i modulation, which is discussed later.

TRPM6 (ENSG00000119121; *TRPM6*) and TRPM7 (ENSG00000092439; *TRPM7*) are highly homologous channel kinases, with expression in the kidney and intestine for TRPM6 and ubiquitously for TRPM7 (Runnels et al. 2001; Monteilh-Zoller et al. 2003; Voets et al.

2004b). TRPM6 is highly permeable to Mg²⁺, activated by low [Mg²⁺]_i, and is shown to be important in the Mg²⁺ homeostasis and reabsorption in the kidney and intestine (Schlingmann et al. 2002; Voets et al. 2004b; Schlingmann et al. 2005). Apart from Mg²⁺ and Ca²⁺, TRPM7 is also permeable to divalent cations and is responsible for the uptake of these trace metal ions (Monteilh-Zoller et al. 2003). Furthermore, TRPM7 is shown to be involved in the regulation of the cell cycle and in neurotoxic death (Wolf and Cittadini 1999; Aarts et al. 2003; Aarts and Tymianski 2005). Zebrafish with a TRPM7 mutation have a defective skeletogenesis with kidney-stone formation and have an increased cell death of the melanophores (Elizondo et al. 2005; McNeill et al. 2007).

TRPM8 (ENSG000000144481; *TRPM8*) cDNA was isolated from prostate cancer cells, but was later shown to be widely expressed, with high expression in a subset of pain- and temperature-sensitive neurons (Tsavaler et al. 2001; McKemy et al. 2002; Peier et al. 2002a). TRPM8 is activated by cold temperatures (8–28°C) and by chemicals such as icilin and menthol, known to produce a cooling sensation (Voets et al. 2004a; Dhaka et al. 2006). Although the role for TRPM8 in the progression of cancer cells is highly debated, it is clear that it acts as a cold thermosensor in sensory neurons.

TRPA

TRPA1 (ENSG00000104321; *TRPA1*) is the only member of the TRPA (ankyrin) family characterized by the 14 NH₂ terminal ankyrin repeats (Story et al. 2003). It is expressed in hair cells and in the sensory DRG and TG neurons (Story et al. 2003; Corey et al. 2004). TRPA1 is activated by noxious cold and different chemicals including allyl isothiocyanate (the pungent compound in mustard oil), allicin (from garlic), cinnamaldehyde (from cinnamon), mentol (from mint), tetra-hydrocannabinoid (from marijuana), nicotine (from tobacco) and bradykinin (Patapoutian et al. 2003; Story et al. 2003; Macpherson et al. 2005; Karashima et al. 2007; Macpherson et al. 2007; Karashima

et al. 2009; Talavera et al. 2009). TRPA1 plays an important role in cold temperature and chemical-induced nociception and in the transduction mechanism through which these irritants and other endogenous proalgesics elicit inflammatory pain (Story et al. 2003; Bautista et al. 2006; Kwan et al. 2006; Karashima et al. 2009). TRPA1 is also suggested as an interesting target for the treatment of cough in humans, as TRPA1 agonists can evoke coughing, an effect that is reduced in the presence of TRPA1 antagonists (Andre et al. 2009; Birrell et al. 2009).

TRPPs

The TRPP (polycystin) family comprises eight members, from which only the polycystic kidney disease 2 (PKD2 or TRPP2) and the PKD2-like (TRPP3 and TRPP5, or, according to Clapham et al. 2009, named TRPP1, TRPP2, and TRPP3) are shown to be channels. The cation-permeable TRPP channels have a P_{Ca}/P_{Na} between 1 and 5 and do not contain a TRP domain nor ankyrin repeats (see Fig. 2) (Delmas 2004; Delmas et al. 2004).

TRPP2 (ENSG00000118762; TRPP2) is widely expressed but most present in the kidney. It is localized to both motile and nonmotile cilia, in which it seems to be a mechanosensor involved in the nodal ciliary movement (Delmas et al. 2004). TRPP2's role in this crucial process for correct organ localization during development is consistent with the left to right asymmetry defects found in animal models lacking TRPP2 (Pennekamp et al. 2002; Bisgrove et al. 2005). Via a coiled-coil domain, TRPP2 and TRPP1 can form a functional polycystin complex, which appears to be essential for pressure-sensing in the kidney, a process altered in autosomal-dominant polycystic kidney disease (Sharif-Naeini et al. 2009).

TRPP3 (ENSG00000107593; TRPP3) and TRPP5 (ENSG00000078795; TRPP5) are less studied, and although TRPP3 is widely expressed, expression of TRPP5 is mainly shown in the testes (Keller et al. 1994; Nomura et al. 1998; Guo et al. 2000). The Ca²⁺-permeable, nonselective TRPP3 channel is shown to be activated by alkalization and, as such, is thought

to be involved in acid-sensing of sour tastes and in the cerebrospinal fluid (Huang et al. 2006; Ishimaru et al. 2006; Shimizu et al. 2009). TRPP5 might play a role in calcium homeostasis and, as such, may contribute to cell proliferation, apoptosis, (Xiao et al. 2009) and to spermatogenesis (Guo et al. 2000; Chen et al. 2008; Xiao et al. 2009).

TRPMLs

The TRPML (mucolipin) family contains three mammalian members: TRPML1 (ENSG00000090674; TRPML1), TRPML2 (ENSG00000153898; TRPML2), and TRPML3 (ENSG0000055732; TRPML3). The TRPML proteins show only low homology with the other TRP channels and are comparatively shorter. As TRPML ion channels are mainly localized in endosomes and lysosomes, their characteristics will be further elucidated below (Cheng et al. 2010b).

TRP CHANNELS DEPOLARIZE EXCITABLE CELLS AND CHANGE INWARDLY-DRIVING FORCES FOR Ca²⁺ ENTRY

Activation of all TRP channels as nonselective cation channels causes a cell depolarization. This depolarizing action of TRP channels is often underestimated. As outlined, many TRP channels have a relatively small fractional Ca²⁺ current. TRPV1, the classical example for TRP-channel-activated Ca²⁺ entry, has only a fractional Ca²⁺ current of less than 5% (Zeilhofer et al. 1997). Also, TRPM8 has a small fractional Ca²⁺ current of ~3%. Only TRPV5, TRPV6, and, in addition, TRPA1 and TRPM3 are characterized by a high fractional Ca²⁺ current. For TRPM3, this fraction is around 24% of the total current and even increases to ~51% in 10 mM Ca²⁺ (Drews et al. 2010). Therefore, next to their role as Ca²⁺-entry channels, it has to be considered that TRPs may have an important function as depolarizing ion channels.

First, TRP function concerns excitable cells expressing voltage-operated Ca²⁺ channels (CaVs, VOCCs) (Fig. 3A). Activation of TRP channels would trigger gating of those channels



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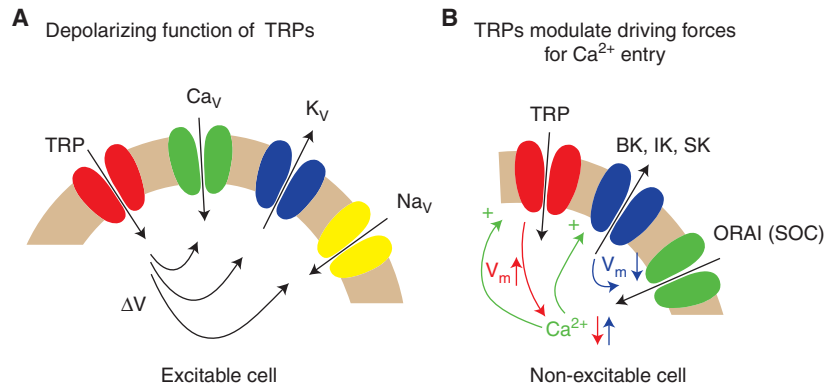


Figure 3. TRP channels depolarize excitable cells and modulate the driving force for Ca^{2+} entry. (A) Depolarization of excitable cells upon opening of TRP channels regulates voltage-dependent Ca^{2+} , K^+ , and Na^+ channels. (B) Membrane depolarization by TRP channels results in a reduced Ca^{2+} entry via ORAI, whereas hyperpolarization of the membrane by BK, IK, or SK channels results in an increased Ca^{2+} influx. This Ca^{2+} then modulates TRP and BK, IK, and SK function to fine-tune the $[Ca^{2+}]_i$ content.

or, if maintained depolarizations are generated, may induce Ca^{2+} -channel inactivation. In addition, the firing pattern of neuronal cells will be modulated by conductance changes via TRP channel activation of inhibition. Examples have been described in detail, indicating that electrogenic effects of TRP channels might be even more important than a direct contribution to $[Ca^{2+}]_i$ changes by mediating Ca^{2+} entry. Only some are mentioned here. All TRPCs are expressed in the brain and obviously have a significant role in regulation of the firing pattern of neurons (Ramsey et al. 2006; Huang et al. 2007; Boisseau et al. 2008; Gokce et al. 2009). They are involved in brain development, synaptogenesis, growth-cone guidance, dendritic growth, spine forming, and many other functions coupled to electrogenesis (Amaral and Pozzo-Miller 2007b; Wen et al. 2007; Tai et al. 2008; for a review, see Talavera et al. 2008; Shim et al. 2009). Persistent neuronal activity lasting seconds to minutes allows the transient storage of memory traces in entorhinal cortex and, thus, could play a major role in working memory. This firing property involves intrinsic properties in cortical neurons by the recruitment of a nonselective cation conductance, probably via heteromeric TRPC channels (TRPC4/5) (Zhang et al. 2010). TRPC3 and

TRPC7 channels are expressed in rhythmically active ventral respiratory group islands in the Pre-Bötzinger complex. TRPC3/7 mediate inward currents underlying the pacemaker activity and enhance respiratory rhythm activity (Ben-Mabrouk and Tryba 2010). TRPC3 in the hippocampus is involved in theta-burst stimulation of mossy fibers (MF). Brief theta-burst stimulation of mossy fibers induced a long-lasting depression in the amplitude of EPSCs mediated by both AMPA and NMDA receptors and a reduction in neurotransmitter release. This depression depends on BDNF-mediated activation of TRPC3, and probably has an electrical component (Amaral and Pozzo-Miller 2007a; Li et al. 2010). It has also been shown that TRPV1 mediates long-term depression, including a Ca^{2+} -independent mechanism (Gibson et al. 2008). In general, TRPV1 seems to be involved in the regulation of LTP and LTD (Li et al. 2008). TRPV1 is involved in the activity-dependent facilitation of glutamatergic transmission from solitary tract (ST) afferents. Afferent activation triggered long-lasting asynchronous glutamate release only from TRPV1-expressing synapses, resulting in postsynaptic EPSCs. This release depends on presynaptic TRPV1s and depolarization-dependent activation of



VOCCs. This interaction provides a new form of synaptic plasticity and brings a new integrative feature to the CNS and autonomic regulation (Peters et al. 2010). Another striking interaction between TRPV1 and VOCC has been shown for the action of TNF- α on nociception, which depends on a TRPV1-induced shift in the membrane potential and a modulation of VOCCs thereupon (mainly N-type, less L- and P-/Q-type) (Hagenacker et al. 2009). Temperature can dynamically influence the hippocampal neural activities. TRPV4 seems to be an important player in this signaling cascade: Activation of TRPV4 depolarizes the resting membrane potential in hippocampal neurons by allowing cation influx and potentiates neuronal firing. This effect is absent in TRPV4-deficient mice and to evoke firing, larger depolarizations are required in these mice. Thus, TRPV4 is a key regulator for hippocampal neural excitabilities, also a Ca²⁺-independent mechanism (Shibasaki et al. 2007).

Several functions of TRP channels involved in the generation of pacemaking inward currents are known. In cardiac muscle, TRPC-mediated inward currents might participate in pacemaking (Ju and Allen 2007). In ileal smooth muscle cell, TRPC4 underlies the muscarinic inward current, which triggers depolarization and the contractile response of these intestinal muscles (Tsvilovsky et al. 2009). Many other examples for a close interaction between TRP channels and VOCC can be found in the literature.

Second, TRP channels can regulate the driving forces for Ca²⁺ entry, mainly in nonexcitable cells, via depolarization (negative-feedback regulation) or hyperpolarization (positive-feedback regulation) via Ca²⁺-dependent activation of other ion channels, such as K⁺ channels (Fig. 3B). Again, many examples are described in detail. For instance, TRPM4 and TRPM5 are both activated by an increase in [Ca²⁺]_i but are impermeable for Ca²⁺. They influence, however, Ca²⁺ entry through Ca²⁺-permeable channels such as the ORAI/STIM complex (CRAC), by decreasing Ca²⁺ entry due to depolarization (for a striking negative-feedback example, see mast cells; Nilius and Vennekens

2006; Vennekens et al. 2007). Inhibition of TRPM4 in mast cells causes cell hyperpolarization following antigen activation of these cells. In turn, the CRAC-mediated Ca²⁺ influx will be increased, resulting in an elevated release of histamine and interleukins and consequently in an aggravated allergic response (Vennekens et al. 2007; Vennekens et al. 2008). Conversely, activation of TRPM4 might be a means to weaken allergic responses. This interaction between depolarizing TRPM4/5 and the hyperpolarization by Ca²⁺-activated K⁺ channels, such as BK_{Ca} (Slo1 or K_{Ca}1.1, K_{Ca}4.1–4.2), IKs (K_{Ca}3.1), and SKs (K_{Ca}2.1–2.3) generates a fine-tuning of Ca²⁺ entry in many nonexcitable cells, such as several blood cell types and endothelial cells. Another striking example is the close interaction and physical association of TRPC1 with BK_{Ca} in vascular smooth muscle cells. Activation of TRPC1 causes hyperpolarization, which in turn could serve to reduce agonist-induced membrane depolarization, thereby preventing excessive contraction of VSMCs to contractile agonists (Kwan et al. 2009). A similar BKCa-TRPC6 association is considered for the dynamic regulation of the filter slit function in podocytes of the renal glomeruli (Kim et al. 2009a).

Third, TRP channels are targets of changes of [Ca²⁺]_i themselves. They can be activated or inhibited by Ca²⁺. Probably the earliest Ca²⁺-activated channel in phylogenies is the yeast mechanosensor TRPY1, in which Ca²⁺ binds to clusters of negative charges in the C-terminus and greatly enhances the force-induced activation (Su et al. 2009). Other TRP channels that are activated by Ca²⁺ include TRPC1, TRPC4, TRPC5, TRPC6, TRPV4, TRPM2, TRPA1, TRPM4, and TRPM5. Many, if not all, TRP channels are modulated by Ca²⁺, often via complex signaling cascades including Ca²⁺/CaM binding, Ca²⁺-dependent PLC modulation, and Ca²⁺-dependent PKC activation (for TRPM4, see Nilius et al. 2005b). Some TRPs have more Ca²⁺-binding sites, often overlapping with PIP2- and especially CaM-binding sites, for which binding domains have been identified in detail for TRPC1 through 7. CaM may also interrupt binding sites for

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many proteins such as MARCKS, GAP43, GRK5, EGFR, and the ErbB family (for a review, see Gordon-Shaag et al. 2008). In addition to Ca^{2+} -dependent activation, all TRP channels show an activity-dependent inactivation mediated by Ca^{2+} , mostly at higher concentrations than needed for activation. Possible mechanisms include Ca^{2+} -dependent kinases; Ca^{2+} -dependent phosphatases; Ca^{2+} -regulated PLCs, which modulate the important TRP-channel modulator $\text{PI}(4,5)\text{P}_2$ (Nilius et al. 2006); and direct interaction with $\text{Ca}^{2+}/\text{CaM}$ (Nilius et al. 2005b; Gordon-Shaag et al. 2008; Nilius et al. 2008). This interplay between Ca^{2+} -dependent activation and inactivation provides a huge diversity of TRP-channel modulation in native cells.

TRP CHANNELS AS INTRACELLULAR CALCIUM-RELEASE CHANNELS

The main dogma so far has been that most of the TRP channels exert their functional effects by their strategic localization in the plasma membrane, where they act as ion channels. Their role as scaffolding proteins or intracellular proteins serving different cell functions has not yet been considered systematically. In fact, most, if not all, TRP channels are also located in intracellular organelles, in which the sarco/endoplasmic reticulum and endosomes, lysosomes, and autophagosomes are only the best-studied compartments. The role of mitochondrial-, Golgi-, nuclear- and peroxisomal-TRP channels is not yet understood. TRP channels can be found in intracellular membranes that form part of the biosynthetic or secretory pathway, mainly, when they are on the way to the plasma membrane. Alternatively, TRP channels may play a role in intracellular organelles, participating in maintaining/establishing vesicular ion homeostasis or regulating membrane trafficking. Following the division of intracellular organelles into two groups (group 1: endocytotic, secretory, and autophagic with ER, Golgi apparatus, secretory vesicles/granules, endosomes, autophagosomes, and lysosomes; and group 2: mitochondria, peroxisomes, and nucleus), all have intraluminal- Ca^{2+}

concentrations much higher than the cytosolic- Ca^{2+} concentrations, ranging from μM to mM (Dong et al. 2010). Therefore, Ca^{2+} homeostasis in these organelles will be a crucial cell function. Increasing evidence points to a role of several TRP channels as intracellular, calcium-release channels, which is the focus of this review. An important problem is that many TRP channels, as discussed above, require $\text{PI}(4,5)\text{P}_2$ for activation (see Rohacs 2007; Rohacs and Nilius 2007; Nilius et al. 2008; Rohacs 2009). Because intracellular membranes lack this phospholipid, it is intriguing to speculate that other substituents may compensate for the requirement of $\text{PI}(4,5)\text{P}_2$ for TRP functioning (Fig. 4).

TRP Channels in Endoplasmic and Sarcoplasmic Reticulum

First, evidence for a role for TRPV1 as an intracellular, calcium-release channel comes from experiments showing that activation of heterologously expressed TRPV1 in COS-7 cells and native TRPV1 in dorsal root ganglion cells gives rise to an increase in intracellular calcium in the absence of extracellular calcium (Olah et al. 2001). It was also already known that a weak agonist of TRPV1, anandamide, induces intracellular calcium release via a PLC-independent mechanism (Felder et al. 1993). Further experiments revealed that TRPV1 is localized to the ER and Golgi compartments. Activation of TRPV1 by capsaicin induces calcium release from an IP_3 -sensitive but thapsigargin-insensitive store (Turner et al. 2003). Calcium gradients in the Golgi are maintained by SERCA and by the thapsigargin-insensitive secretory pathway (SPCA). Intracellular stores can be dissected based on their release and/or refilling capacities; within the IP_3 -sensitive store, there exists a compartment that also contains functional TRPV1 molecules that mediate release. The TRPV1/ IP_3 -containing store is apparently thapsigargin-insensitive. Depletion of this calcium store can occur without I_{CRAC} activation. Due to the thapsigargin-insensitivity of TRPV1-induced calcium release, the most likely location for TRPV1 is in the SPCA-positive

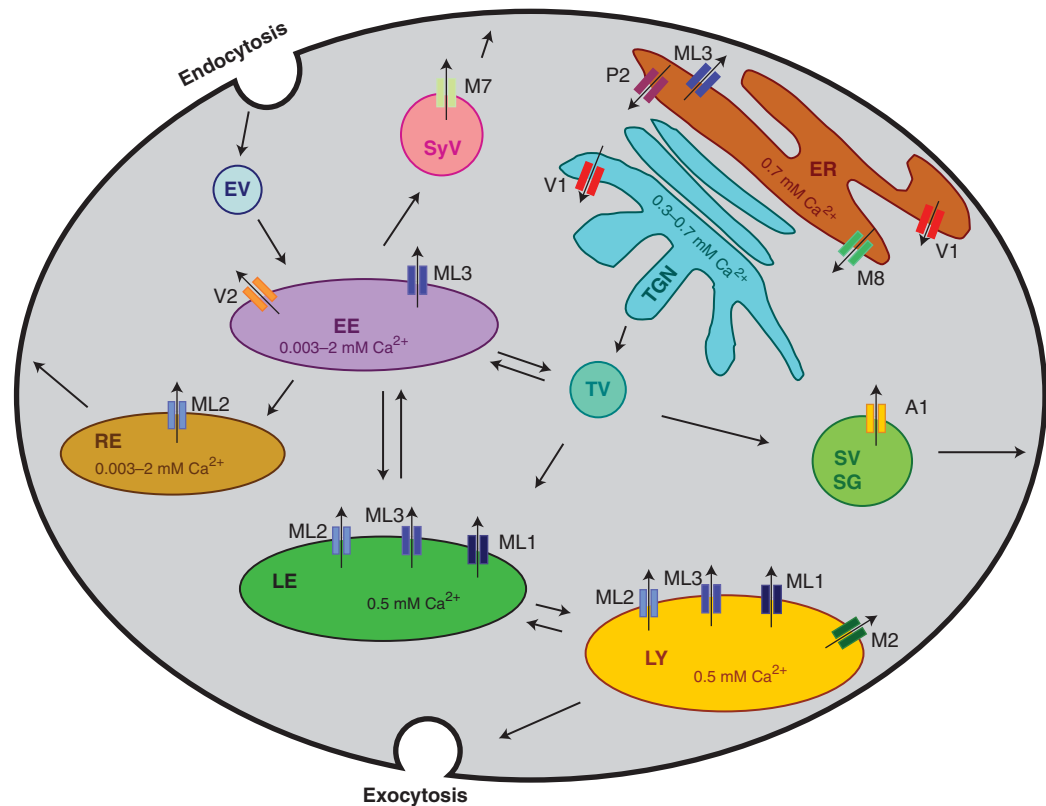


Figure 4. Expression of TRP channels in intracellular compartments. Early endosomes (EE) are derived from the plasma membrane via endocytotic vesicles (EV). The cargo from these early endosomes can either go back to the plasma membrane via the recycling endosomes (RE) or follow the late endocytotic pathway via late endosomes (LE) to the lysosomes (LY). Intermediate transport vesicles (TV) are derived from the ER and/or the trans-Golgi-network (TGN). The content in these transport vesicles can either be delivered to early endosomes, late endosomes, or be transported to the plasma membrane via secretory vesicles (SV) or secretory granules (SG). Synaptic vesicles (SyV) are derived from early endosomes and release neurotransmitters in the extracellular space. Only intracellular locations of TRP channels are indicated.

Golgi compartments (Turner et al. 2003). However, other studies suggest that TRPV1- and thapsigargin-sensitive internal calcium pools substantially overlap, and that TRPV1 immunoreactivity co-localizes with a marker in the ER. Still, although TRPV1 forms agonist-sensitive channels in the ER, which upon activation release calcium from internal stores, it fails to activate endogenous store-operated Ca^{2+} entry (Wisnoskey et al. 2003).

TRPM8 is amongst others expressed in LNCaP (lymph node carcinoma of the prostate) cells and sensory neurons from dorsal root and trigeminal ganglia (McKemy et al. 2002; Zhang

and Barritt 2004; Thebault et al. 2005; Ramsey et al. 2006). Several lines of evidence suggest that TRPM8 is involved in menthol-induced calcium release from intracellular stores. TRPM8 is shown to be expressed in both the endoplasmic reticulum and the plasma membrane of the androgen-responsive prostate cancer LNCaP cells and to mediate, respectively, Ca^{2+} inflow and Ca^{2+} release from intracellular stores in these cells (Zhang and Barritt 2004). These cells show a current in response to cold and menthol with biophysical properties (strong inward rectification and high calcium selectivity) different than those described for

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TRPM8 in a heterologous expression system and in sensory neurons (Thebault et al. 2005). This current could nevertheless be suppressed by experimental maneuvers that decrease endogenous TRPM8 mRNA or protein, which is explained by the extraplasmalemmal localization of TRPM8 in these cells. Indeed, TRPM8 in the ER from LNCaP cells is able to support Ca^{2+} release in response to cold or menthol, and this ER Ca^{2+} store depletion activates Ca^{2+} entry via plasma membrane store-operated channels (SOC) (Thebault et al. 2005). However, the fact that TRPM8 is responsible for the menthol-induced calcium release is controversial. Indeed, experiments in different cell lines (HEK293, LNCaP, CHO, and COS cells) indicate that the menthol-induced calcium release is potentiated at higher temperatures (Mahieu et al. 2007). Furthermore, overexpression of TRPM8 does not enhance the menthol-induced calcium release; icilin and eucalyptol, 2 more potent agonists of TRPM8 than menthol, do not induce calcium release, unlike geraniol and linalool, which are structurally related to menthol. These data indicate that menthol induces intracellular calcium release in a TRPM8-independent manner. Clearly, more experiments are needed to unravel the molecular identity of this calcium-release channel.

Trpp2 and *Pkd1*, or polycystin-1, are genes mutated in autosomal-dominant polycystic kidney disease (ADPKD). Both proteins are expressed in many tissues, including kidney, heart, liver, pancreas, brain, and muscles (Hughes et al. 1995; Geng et al. 1997; Luo et al. 2003). PKD1 is a large glycoprotein localized to the plasma membrane and primary cilia (Hanaoka et al. 2000; Newby et al. 2002; Yoder et al. 2002). TRPP2 has a dynamic expression pattern with localization reported in mitotic spindles, the ER/SR, basolateral plasma membrane, and together with PKD1 in the primary cilium (Cai et al. 1999; Foggensteiner et al. 2000; Yoder et al. 2002; Rundle et al. 2004). Expression of TRPP2 in the ER is caused by ER-retention signals in the cytoplasmic tail, which will prevent trafficking of TRPP2 toward the plasma membrane (Cai et al. 1999; Hanaoka

et al. 2000). Masking or deleting this ER-retention motif allows plasma membrane expression of TRPP2 (Cai et al. 1999). Co-immunoprecipitation experiments show that polycystin-1, which is present at the plasma membrane, is physically associating with polycystin-2 (Tsiokas et al. 1997). This might mean that TRPP2 can function as a surface membrane calcium-permeable channel or signaling complex, chaperoned by TRPP1 (Hanaoka et al. 2000). On the other side, TRPP2 may be located in the ER, tethering close to the surface membrane via the physical association with TRPP1 (Koulen et al. 2002). Single channel recordings from ER microsomes fused to lipid bilayers reveal that polycystin-2 is a high conductance channel that is permeable to divalent cations (Koulen et al. 2002). It functions as a calcium-release channel in a porcine kidney cell line (LLC-PK1) to augment calcium transients initiated by the IP_3 receptor after receptor stimulation by, for example, vasopressin. This calcium release does not seem to require coassembly with polycystin-1. Cells expressing a mutant channel protein, which retains the protein interactions with wild-type polycystin-2, do not show this calcium release, strongly indicating that TRPP2 itself forms the channel (Koulen et al. 2002), in contrast with the polycystin-1-dependent channel activity of TRPP2 at the plasma membrane (Hanaoka et al. 2000). TRPP2 can be activated by intracellular calcium; it shows a bell-shaped response curve to Ca^{2+} that is dependent on phosphorylation at the C-terminus of the protein (Cai et al. 2004). These data suggest that TRPP2 functions as a new type of calcium-release channel, with properties (ER location, calcium-dependent calcium-channel activity) allowing it to mediate calcium-induced calcium release. Recent data suggest that the function of TRPP2 as a calcium-induced calcium-release channel is dependent on interaction with the IP_3 receptor, and that TRPP2 is activated by a local rise in cytosolic Ca^{2+} generated by IP_3 -induced calcium release (Sammels et al. 2010). The pathomechanism by which the TRPP2 channel, together with PKD1, contributes to ADPKD is still not completely understood. In the primary





cilium, the TRPP2/PKD1 complex acts as a mechanosensor that provides flow-activated Ca²⁺ entry and plays a role in Ca²⁺ signaling in tubular renal cells. This mechanosensitive property of the complex is deficient in PKD1-deficient cells. Additionally, the PKD1/TRPP2 complex regulates transfer of the helix-loop-helix (HLH) protein Id2, a crucial regulator of cell proliferation and differentiation, into the nucleus. An enhanced nuclear localization of Id2 in renal epithelial cells from AKPKD patients constitutes a mechanism for the hyperproliferative phenotype and may cause cyst formation (Benezra 2005; Li et al. 2005). Furthermore, TRPP2 may play a role in the increased apoptotic rate reported in ADPKD patients and several models of polycystic kidney diseases. Indeed, the Ca²⁺ content of the ER determines the sensitivity of the cell to apoptotic stress, and TRPP2 is suggested to function as an antiapoptotic ion channel that regulates the Ca²⁺ concentration in the ER (Wegierski et al. 2009).

TRP Channels in Endosomes and Lysosomes

The endolysosome system is comprised of early endosomes, recycling endosomes, late endosomes, and lysosomes (Luzio et al. 2007b; Dong et al. 2010). Early endosomes are derived from the plasma membrane via endocytosis. Components in these early endosomes can either be recycled back to the plasma membrane via the recycling endosomes or follow the late endosome pathway. Lysosomes are derived from late endosomes and are filled with hydrolytic enzymes. Some common features of endolysosomes are an acidic pH (established and maintained by the vacuolar (V)-ATPase H⁺ pump and essential for the degradative function of the hydrolases) and a positive membrane potential (assumed to be in the range of +30 to +110 mV) that provides a driving force for calcium release into the cytosol. Indeed, endolysosomes also serve as storage for intracellular calcium, containing a luminal calcium concentration of ~0.5 mM that is maintained by an unidentified H⁺-Ca²⁺ exchanger. Next to other factors, such as small GTPase Rabs and

phosphoinositides (PIP), membrane trafficking is regulated by the release of calcium from endolysosomes. In fact, the membrane fusion process that drives the movement of endocytosed material and enzymes within the endocytic pathway depends on calcium ions, presumably released from the endocytic organelles (Pryor et al. 2000). However, the ion channels responsible for endolysosomal calcium release are still undefined. Candidates include several members of the TRP family, such as TRPMLs, TRPV2, and TRPM2.

TRPMLs, or mucolipins, constitute a family of inwardly-rectifying, calcium-permeant, but probably proton-impermeant, cation channels and consist of three members: TRPML1, TRPML2, and TRPML3. All TRPMLs colocalize with lysosome-associated membrane protein (Lamp-1) or Rab7, indicating localization to late endosomes and lysosomes (Karacsonyi et al. 2007; Thompson et al. 2007; Kim et al. 2009b; Martina et al. 2009). In addition, TRPML2 is found in recycling endosomes (Karacsonyi et al. 2007), whereas TRPML3 also localizes to early endosomes and the plasma membrane (Kim et al. 2009b). However, it has been shown that TRPMLs interact to form homo- and heteromultimers, and that the presence of either TRPML1 or TRPML2 specifically influences the spatial distribution of TRPML3. Indeed, TRPML1 and TRPML2 homomultimers form lysosomal proteins, whereas TRPML3 homomultimers are probably channels in the endoplasmic reticulum. However, TRPML3 localizes to lysosomes when coexpressed with either TRPML1 or TRPML2, and is comparably mislocalized when lysosomal targeting of TRPML1 and TRPML2 is disrupted. Conversely, TRPML3 does not cause retention of TRPML1 or TRPML2 in the endoplasmic reticulum. These data demonstrate that there is a hierarchy controlling the subcellular distributions of the TRPMLs, such that TRPML1 and TRPML2 dictate the localization of TRPML3 and not vice versa (Venkatachalam et al. 2006).

TRPML1 (or Mucolipin 1) is the best described member of the TRPML subfamily and is expressed in almost every tissue with the highest level of expression in the brain, kidney,

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spleen, liver, and heart (Sun et al. 2000). TRPML1 follows a direct or indirect pathway to reach lysosomes. Newly synthesized proteins, together with TRPML1, are routed directly from the Golgi to lysosomes by recognition of the N-terminal E¹¹TERLLL motif of TRPML1 (direct pathway). The indirect pathway comprises trafficking to the plasma membrane, followed by internalization to early endosome that is guided by the C-terminal E⁵⁷³EHSLL motif (Curcio-Morelli et al. 2009; Samie et al. 2009). TRPML1 is a TRP-channel-related protein that shows strong topological homology with the polycystin-2 channel and contains an internal Ca²⁺- and Na⁺-channel-pore region (Sun et al. 2000). Several studies suggest that TRPML1 is a nonselective cation channel with a large conductance and permeability to Na⁺, K⁺, and Ca²⁺ (LaPlante et al. 2002; Raychowdhury et al. 2004). However, its localization in the endolysosomal membrane makes it difficult to characterize. TRPML3 is the only TRPML channel found in the plasma membrane, making it easier to characterize the channel properties via whole-cell current measurements. This revealed that TRPML3 is an inwardly rectifying, Ca²⁺-permeable cation channel (Cuajungco and Samie 2008). The current is inhibited by an acid extracytosolic (analogous to the luminal side) pH (Kim et al. 2008). Notably, elimination of TRPML3 regulation by extracytosolic pH has the same functional and cellular phenotype as the A419P (Va) mutation, a gain-of-function mutation that causes the varitint-waddler phenotype (a disease characterized by deafness, circling behavior, and pigmentation defects) (Di Palma et al. 2002). This mutation is likely to disrupt channel-gating by locking the channel in an open state, making the channel constitutively active and yielding much larger currents (Cuajungco and Samie 2008); although basic properties, such as I-V characteristics, single channel conductance, and ion selectivity have not changed (Kim et al. 2007; Nagata et al. 2008). The same mutation has been made in TRPML1 and TRPML2 channels in order to effectively characterize the pore properties of these channels using whole-cell recordings. This revealed, for both channels, inwardly

rectifying, Ca²⁺-permeable cation currents, in accordance with TRPML3 channel properties (Dong et al. 2009; Samie et al. 2009). At least for TRPML1, several properties of this mutated channel, such as IV relationship, kinetics, and voltage dependence, are similar to the wild-type channel measured in the lysosomal membrane (Dong et al. 2008), indicating that the activating Va mutation is a useful approach for characterizing the pore properties of TRPML1. Obviously, these channels provide a novel class of TRP channels that are functionally still much less characterized than other TRPs (for an excellent review, see Cheng et al. 2010b; Dong et al. 2010).

The physiological functions of the TRPML channels are still under intensive investigation. Mucolipins could regulate the ionic conditions within, and acidity of, the endocytic organelles, in this way regulating the activity and delivery of the digestive enzymes within the endocytic pathway (Puertollano and Kiselyov 2009). However, the calcium permeability of TRPML channels allows a role in different intracellular processes regulated by calcium. Mutations in the *Trpml1* gene cause mucopolidosis type IV, a lysosomal storage disease characterized by severe psychomotor retardation and ophthalmologic abnormalities. Indeed, all cell types show an abnormal accumulation of phospholipids, sphingolipids, acidic mucopolysaccharides, and cholesterol in swollen and enlarged LEL-like vacuoles (Puertollano and Kiselyov 2009). In agreement with this, cells from *Trpml1* KO mice show abnormal lipid accumulation and enlarged vacuoles (Venugopal et al. 2007). These enlarged LELs seem to be the late endosome-lysosome hybrid organelles from which lysosomes are formed in the normal situation. Enlarged endolysosomes can result from either uncontrolled and excessive fusion, defective membrane fission, or impaired organellar osmoregulation (Luzio et al. 2007a). The defect observed in *Trpml1*-deficient cells is most likely related to the sorting and trafficking processes of the endocytic pathway, more specifically the formation of transport vesicles from the LEL compartment to the trans-Golgi-network and the reformation of lysosomes from the late

endosome-lysosome hybrid organelles (Thompson et al. 2007). The Ca²⁺ permeability of TRPML1 seems to be required for the membrane fission from LEL compartments or late endosome-lysosome hybrids and the biogenesis of both late retrograde transport vesicles and lysosomes. Indeed, membrane fission and stabilization of transport vesicles are dependent on luminal calcium and intraluminal calcium release (Luzio et al. 2007a). The major mucopolidosis type IV disease mutations of TRPML1 are expected to produce no protein (Altarescu et al. 2002). However, two mutations (V446L and ΔF408) do retain TRPML1 channel function. WT TRPML1 is inhibited by a reduction of pH, and this pH-dependent regulation seems to be lost in these two mutations (Raychowdhury et al. 2004). The recent generation of the *Trpml1* KO mouse, a murine model for MLIV, will help to further elucidate the function of TRPML1 (Venugopal et al. 2007). Interestingly, a *Drosophila* model for mucopolidosis type IV has been developed that mimicks some of the key disease features, such as abnormal intracellular accumulation of macromolecules, motor defects, and neurodegeneration. Here, the basis for macromolecule retention is a defective autophagy, which results in oxidative stress and impaired synaptic transmission. Late-apoptotic cells accumulate in the brains of *trpml-* (the only TRPML member in the fly) deficient flies. The accumulation of those cells, and also the degree of motor deficits, were suppressed by expression of TRPML in neurons, glia, and hematopoietic cells. Because hematopoietic cells in humans are involved in clearance of apoptotic cells, it seems possible that bone marrow transplantation might have a potential as a new therapeutic strategy for MLIV (Venkatachalam et al. 2008).

TRPML1 is also thought to mediate a NAADP-activated intracellular calcium release channel. Indeed, nicotinic acid adenine dinucleotide phosphate (NAADP) is an attractive candidate for mediating endolysosomal calcium release (Churchill et al. 2002; Calcraft et al. 2009). In fact, a lysosomal NAADP-sensitive Ca²⁺-release channel, different from sarcoplasmic reticulum Ca²⁺-release channels, could

be measured in lysosomes from native rat liver cells and bovine coronary arterial myocytes (Zhang and Li 2007; Zhang et al. 2009). This current could be blocked by using an anti-TRPML1 antibody or a TRPML1-specific siRNA, suggesting involvement of TRPML1. However, the molecular identity of the NAADP receptor remains controversial (Galione and Churchill 2002). Another attractive family of ion channels comprises the two-pore channel family (TPCs) (Patel et al. 2010). Indeed, these channels provide a family of NAADP receptors, with TPC1 and TPC3 being expressed on endolysosomal and TPC2 on lysosomal membranes (Calcraft et al. 2009). Both TPC1 and TPC2 have been shown to be an important component of NAADP-elicited calcium release (Braloiu et al. 2009; Zong et al. 2009). Thus, the nature of the NAADP-receptor and the contribution of different ion channels to NAADP action remains a matter of debate.

Much less is known about the function of TRPML2 and TRPML3. TRPML2 is expressed in B-lymphocytes at different cell stages. Overexpression of TRPML2 in these cells induces accumulation of enlarged lysosomal structures, indicating that TRPML2 might participate in the regulation of the specialized lysosomal compartment of B-lymphocytes, and in this way may be critical for normal immune response (Song et al. 2006). Furthermore, TRPML2 has been reported to have a regulatory role in the trafficking of proteins along the Arf6-regulated pathway. Indeed, TRPML2 colocalizes with glycosylphosphatidylinositol-anchored proteins (GPI-APs), such as CD59, and overexpression of a TRPML2 inactive mutant decreases recycling of CD59 to the plasma membrane, indicating that TRPML2 localizes to the Arf6-regulated pathway and regulates sorting of GPI-APs (Karacsonyi et al. 2007). Overexpression of TRPML3 leads to reduced constitutive and regulated endocytosis, increased autophagy, and marked exacerbation of autophagy evoked by various cell stressors with nearly complete recruitment of TRPML3 into the autophagosomes (Kim et al. 2009b). These data indicate that TRPML3 is a prominent regulator of endocytosis, membrane trafficking, and autophagy, perhaps by

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controlling the Ca^{2+} in the vicinity of cellular organelles that is necessary to regulate these cellular events (Kim et al. 2009b). Furthermore, calcium release from endolysosomes by TRPML3 may be important for efficient endosomal acidification. Indeed, after internalization from the plasma membrane, the endosomes contain a high concentration of calcium that is rapidly released in order to allow acidification of the compartment. TRPML3 is a good candidate to mediate this efflux, since the channel is inhibited by low pH and would still be active at the characteristic pH of the early endosomes, but will become inactive once the acidification has taken place, in this way preventing further Ca^{2+} efflux and acidification (Martina et al. 2009). Given the clinical importance of TRPMLs, these channels obviously define a new group of pharmacological targets as introduced recently by small molecule activators of TRPML3 (Grimm et al. 2010).

TRPV2 localizes to early endosomes, and activation of TRPV2 in these intracellular vesicles is suggested to cause calcium-dependent fusion between endosomal membranes (Saito et al. 2007). Endogenous ionic currents measured in an isolated enlarged endosome showed pharmacological similarities (inhibition by Ruthenium Red and activation by 2-aminoethyl diphenyl borate) with the TRPV2 channel. This current was inhibited by a decrease in the luminal pH and an increase in the luminal chloride concentration, two features known to occur after endocytosis (Saito et al. 2007). The current hypothesis is that activation of TRPV2 leads to Ca^{2+} -dependent fusion between endosomal membranes. Further experiments are needed to confirm this theory.

TRPM2 serves a dual role as a plasma membrane Ca^{2+} -influx channel and as an intracellular, calcium-release channel in pancreatic beta cells (Lange et al. 2009). Indeed, intracellular ADPR elicits intracellular calcium release in these cells, which is dependent on TRPM2 channels and comes from lysosomes. The lysosomal calcium release through TRPM2 contributes to H_2O_2 -mediated beta cell death (Lange et al. 2009).

TRP Channels in Secretory Vesicles, Secretory Granules, and Synaptic Vesicle

Much less is known about TRP channels in these compartments. TRPA1 is expressed in secretory vesicles and granules (Dong et al. 2010). Icilin, a TRPA1 agonist, elicits intracellular Ca^{2+} release from secretory vesicles in HEK cells heterologously expressing TRPA1 (Prasad et al. 2008). TRPA1 is a Ca^{2+} -activated channel (Zurborg et al. 2007) and may therefore contribute to Ca^{2+} release from these organelles. TRPM7 is localized in synaptic vesicles of sympathetic neurons and bound to several proteins of the synaptic vesicle fusion apparatus, including synapsin I and synaptotagmin I. Furthermore, ion conductance via TRPM7 is critical to neurotransmitter release upon an increase in $[\text{Ca}^{2+}]_i$; and might in this way play a role in forming the exocytotic machinery (Krapivinsky et al. 2006). Finally, the role of TRP channels in intracellular organelles is a just-appearing and extremely challenging topic.

CONCLUSIONS

TRP channels have been extensively reviewed in the last 10 years. It is obvious now that they function not only as polymodal cell sensors in sensory processes, but that they are unique channels involved in many cell functions. We want to stress in this review that TRP channels are not only important for Ca^{2+} entry via the plasma membrane. This function might even be overestimated, given the often very small fractional Ca^{2+} currents through these channels. They obviously play an important role in electrogenesis, regulating the activity for voltage-dependent ion channels including Ca^{2+} channels (Ca_v 's, VOCCs). They are also important regulators of the driving forces for Ca^{2+} entry via other Ca^{2+} -permeable channels such as ORAIs, CNG, and NMDA receptors. TRPs must also be considered as targets of changes in $[\text{Ca}^{2+}]_i$, which again creates a huge diversity and versatility of these channels in the whole process of Ca^{2+} signaling. Finally, TRPs are intracellular channels, and may even act in some cases as scaffolding proteins forming signaling complexes. Their role as intracellular

channels is just emerging and will undoubtedly be the focus of future research.

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