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International Union of Pharmacology. XLIX. Nomenclature and Structure-Function Relationships of Transient Receptor Potential Channels

DAVID E. CLAPHAM, DAVID JULIUS, CRAIG MONTELL, AND GÜNTER SCHULTZ

Howard Hughes Medical Institute, Children's Hospital, Boston, Massachusetts (D.E.C.); Department of Cellular and Molecular Pharmacology, University of California, San Francisco, California (D.J.); Department of Biological Chemistry, The Johns Hopkins University School of Medicine, Baltimore Maryland (C.M.); and Institut für Pharmakologie, Charité–Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany (G.S.)

Introduction

The transient receptor potential (TRP[1]) ion channels are named after the role of the channels in *Drosophila* phototransduction. The mammalian genes are encoded by at least 28 channel subunit genes (Fig. 1) (Clapham, 2003; Moran et al., 2004). Six protein families comprise the mammalian TRP superfamily: the classic TRPs (TRPCs), the vanilloid receptor TRPs (TRPVs), the melastatin or long TRPs (TRPMs), the mucolipins (TRPMLs), the polycystins (TRPPs), and ankyrin transmembrane protein 1 (ANKTM1, TRPA1). The TRP channel primary structures predict six transmembrane (TM) domains with a pore domain between the fifth (S5) and sixth (S6) segments and both C and N termini presumably located intracellularly (Vannier et al., 1998). With the exception of some polycystins, TRPs are generally assumed to have six TM domains. This architecture is a common theme for hundreds of ion channels present in life forms ranging from bacteria to mammals.

Despite the topographic similarities between the TRPs and the voltage-gated potassium channels, the TRPs are actually only distantly related to these channels. TRPs are found in eukaryotes from yeast to mammals, often functionally associated with G protein-coupled and growth factor (tyrosine kinase) receptors and phospholipase C (PLC) (Clapham, 2003). Other features include a 25-amino acid (aa) motif in some subfamilies (the TRP domain) containing a TRP box (EWKFAR) just C-terminal to S6. The TRP domain and box, as well as slight variations of these motifs, are present in all TRPC and TRPM channel genes, but not in other TRP channels. The N-terminal cytoplasmic domains of TRPC, TRPV, and TRPA channels contain ankyrin repeats, whereas those of the TRPC and TRPM channels contain proline-rich sequences in the region just C-terminal portion of the TRP domain, referred to as TRP box 2 (Montell, 2005). At present, no features, other than overall 6TM architecture/homology and cationic permeability, define the TRP family. Thus the definition of TRP channels will evolve as functions and structures are clarified.

Genes for the TRP ion channel subunits were first defined in the *Drosophila* visual system. In the *trp* mutant, the light response (receptor potential) decays during prolonged exposure to light. TRP-deficient flies are blinded by intense light because sustained Ca^{2+} entry via TRP ion channels and subsequent Ca^{2+}-dependent adaptation is disrupted. Three genes (*TRP, TRPL,* and *TRP*γ) encode TRP channels that are involved in fly vision, but there are at least 13 TRP-like genes in *Drosophila*. Genetic approaches in flies have not resolved the mechanism of TRP activation, but confirm the importance of PLCβ and other components of the phosphatidylinositol pathway (Hardie et al., 2001; Minke and Cook, 2002; Hardie, 2003; Montell, 2003).

Structural Features

Six TM channels have two "domains," one (S1–S4) containing the S4 voltage sensor and a second (S5–S6) containing the 2TM pore and gate. A high-resolution structure of a TRP channel has not yet been solved. However, the 2TM structure of a bacterial K^+ channel (KcsA) is analogous to the S5 and S6 domains joined by a short pore α helix of the 6TM architecture (Doyle et al., 1996). The KcsA channel is a tetramer of 2TM α helices. The helices corresponding to S5 face the lipid membrane whereas the helices corresponding to S6 line the pore. At both inner and outer membrane faces, layers of aromatic amino acids form a cuff around the pore. In KcsA, the

Address correspondence to: Dr. David E. Clapham, Howard Hughes Medical Institute, Children's Hospital, 1309 Enders Bldg., 320 Longwood Ave., Boston, MA 02115. E-mail: dclapham@enders.tch.harvard.edu

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[1] Abbreviations: TRP, transient receptor potential; TRPC, classic TRP; TRPV, vanilloid receptor TRP; TRPM, melastatin or long TRP; TRPML, mucolipin TRP; TRPP, polycystin TRP; TRPA, ankyrin TRP; TM, transmembrane; PLC, phospholipase C; aa, amino acid; PIP_2, phosphatidylinositol 4,5-bisphosphate; IP_3, inositol 1,4,5-trisphosphate; DAG, diacylglycerol; PKD, polycystic kidney disease; 2-APB, 2-aminoethoxydiphenylborate; PKC, protein kinase C; SKF96365, 1-(β-[3-(4-methoxyphenyl)propoxy]-4-methoxyphenethyl)-1*H*-imidazole.

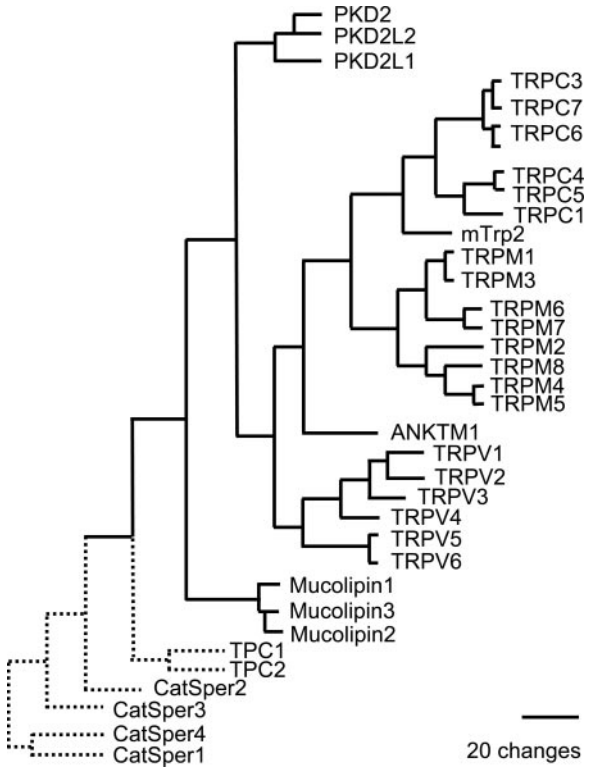

FIG. 1. Alignment of human TRP family proteins using maximum parsimony analysis of the minimal pore regions. The tree was rooted to the bacterial NaChBac (not shown). The CatSper and TPC channels are discussed in "International Union of Pharmacology. L. Nomenclature and Structure-Function Relationships of CatSper and Two-Pore Channels." Figure modified slightly from Yu and Catterall (2004).

selectivity filter is a narrow region near the outer face of the membrane lined by the carbonyl backbone of five conserved amino acids. These amino acids are not present as a group in the largely nonselective TRP channels. Presumably as in KcsA, the S6 segment lines the rest of the channel on its way to the cytoplasm. The S6 segment and the C-terminal amino acids extending into the cytoplasm are the most conserved between the TRP subfamilies and where the gating features of TRP channels are likely to emerge.

One 6TM channel subunit structure for the bacterial K_V channel, *Aeropyrum pernix*, has been determined (Jiang et al., 2003). Flexibility around the S4–S5 linker required that Fab fragments be used to stabilize the protein to form a crystal. The structure was obviously deformed by the Fab fragments, flattening the S1–S4 segment and somewhat disordering the S1 and the N termini. The structure showed that the S3 helix split, with its distal portion (S3b) forming a hairpin loop with S4. For this voltage-gated channel, MacKinnon proposed that the S3b–S4 "paddle" moves from the inner to the outer membrane upon depolarization and pulls on the S5 helix to open the gate. Although the paddle model is currently debated, the general structure of 6TM TRPs is expected to resemble that of *A. pernix* and related structures that emerge.

Channels are opened or closed (gated) by conformational changes in the channel protein. K^+ channels have two gates (upper and lower). Both gates must be open to conduct ions through the pore. Cells normally impart a high voltage (and thus energy) across the protein at rest (e.g., −70 mV) to hold it in its closed state. When this voltage is removed (depolarization), the protein relaxes into an open configuration (its low-energy state). The change in energy needed for gating can also be imparted by changes in temperature, chemical binding, or alteration of the channel protein [see *Discussion* in Clapham (2003)]. In practical usage, voltage-gating refers to channel opening that results from movement of the charged S4 segment in K_V/Na_V/Ca_V channels upon a change in transmembrane voltage. TRP channels lack these charged residues in S4, but their gating is affected by voltage changes. For TRPV1, M4, M5, and M8, the TRP channels that are most sensitive to voltage changes, an important question is which residues in the polypeptide chain convey voltage dependence. In general, TRP channel gating is not dominated by voltage but rather is effected by the energy differences accompanying changes in temperature, binding, and voltage. Perhaps a good analogy for TRP channels is the cyclic nucleotide-gated channels that are internal ligand-gated and are only weakly voltage-dependent.

Functional Features

Of the functionally expressed proteins, only TRPV5 and TRPV6 are Ca^{2+}-selective ($P_{Ca}/P_{Na} > 100$). TRPM4b and TRPM5 are monovalent-selective ($P_{Ca}/P_{Na} < 0.05$), whereas all other TRP channels are relatively nonselective. The TRP channels do not have the sharp voltage sensitivity of the characterized channels in the Ca_V and Na_V families. Thus, upon opening, they depolarize cells from their resting membrane potentials (approximately −70mV in most mammalian cells) to around 0 mV. In short, they depolarize cells and raise intracellular Na^+ and usually Ca^{2+}.

Two common signal transduction pathways that regulate the release of intracellular Ca^{2+} are the G protein-coupled and the tyrosine kinase activation of PLC. PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to form inositol 1,4,5-trisphosphate (IP_3) that opens the IP_3 receptor and liberates Ca^{2+} from the endoplasmic reticulum (Clapham, 1995). Accompanying these chains of events and not necessarily linked to Ca^{2+} store (endoplasmic reticulum) depletion is activation of the TRP channels. The details of these mechanisms are incompletely understood at present. The strongest associations between the phosphatidylinositol pathway and TRP channels involve PLCβ and PIP_2. In *Drosophila* TRP channels, elements of these signal transduction pathways are linked by the scaffolding protein, INAD (Montell, 2003). In mammalian cells, this scaffolding

function may be carried out by PLCγ (Patterson et al., 2002), Homer (Yuan et al., 2003), or other proteins.

Emptied Ca^{2+} stores (endoplasmic reticulum) somehow gate entry of external Ca^{2+} to replenish the deficit (Putney, 1977). The physiological hallmark of the store-operated Ca^{2+} entry process is a large receptor-mediated transient $[Ca^{2+}]_i$ increase followed by a prolonged high $[Ca^{2+}]_i$ plateau phase, dependent on $[Ca^{2+}]_o$. From their first identification in mammalian cells, TRPs were major suspects for the proteins comprising store-operated channels. However, most TRP channels that have been studied in detail are not gated by the usual manipulations defined as activating store-operated Ca^{2+} entry. Thus it is not accurate to refer to TRP channels as store-operated channels, although it may turn out that one or more of these channels participate in this process.

Classification and Nomenclature

In this article, the focus is on the TRP channels encoded by mammalian genes and the nomenclature system adopted by a number of workers in the field (Montell et al., 2002; Clapham, 2003).

The TRPC Channels

The TRPC family can be divided into three subgroups by sequence homology as well as functional similarities: C1/C4/C5, C3/C6/C7, and C2. TRPC1 was the first member of the mammalian TRP family purported to form an ion channel (Zitt et al., 1996). Given the widespread expression of TRPC1 and its ability to coassemble with other TRPC subunits (Xu et al., 1997; Lintschinger et al., 2000; Strübing et al., 2001), TRPC1 might be a component of different heteromeric TRP complexes. The subgroup most closely related to TRPC1 comprises TRPC4 and TRPC5. TRPC4 and TRPC5 are PDZ motif-containing proteins that can form homomeric cation channels that are activated following stimulation of G_q-coupled receptors (Okada et al., 1999; Schaefer et al., 2000) as well as receptor tyrosine kinases (Schaefer et al., 2000). Coexpression of TRPC1 and TRPC4 or TRPC5 results in a nonselective cation channel with negative slope region depolarized to 0 mV. The details of the activation mechanism remain elusive, but the two primary products of PLC enzyme activity, IP_3 and diacylglycerol (DAG), do not activate TRPC4 and TRPC5 (Hofmann et al., 1999; Schaefer et al., 2000). Both TRPC4 and TRPC5 contain a C-terminal PDZ-binding motif (VTTRL). PDZ domain scaffolding proteins, such as the Na^+/H^+ exchanger regulatory factor (NHERF) as well as signaling molecules such as PLCβ1, coimmunoprecipitate with TRPC4 and TRPC5 (Tang et al., 2000), indicating that the channels may be part of multimolecular signaling complexes similar to that in *Drosophila* photoreceptors. Growth factor stimulation initiates the rapid translocation of the transient receptor potential ion channel, TRPC5, from vesicles held in reserve just under the plasma membrane. This process, requiring PI3K, Rac1, and PI(4)K5, affects neurite extension rates in cultured hippocampal neurons and may be a general mechanism for initiating Ca^{2+} influx and cell morphological changes in response to stimuli (Greka et al., 2003; Bezzerides et al., 2004).

Less information is available about TRPC2, which shares approximately 30% sequence identity with the TRPC3/6/7 subfamily. Full-length TRPC2 mRNA and several N-terminal splice variants have been found in mouse and rat tissue, but TRPC2 seems to be a pseudogene in humans (Vannier et al., 1999; Liman, 2003). TRPC2 protein was localized to neuronal micovilli in rat vomeronasal organ (Liman, 2003) and in the head of mouse sperm (Jungnickel et al., 2001). TRPC2-deficient mice display abnormal mating behavior, consistent with a role for this channel in pheromone signaling (Stowers et al., 2002). Zufall and colleagues identified a DAG-gated TRPC2-dependent current in vomeronasal organ sensory neurons, suggesting that TRPC2 underlies neuronal excitability in pheromone sensing (Lucas et al., 2003).

TRPC3, TRPC6, and TRPC7 are ~75% identical. When expressed they constitute nonselective cation currents that rectify in both the inward (− voltages) and outward (+ voltages) directions. TRPC3, TRPC6, and TRPC7 are inwardly and outwardly rectifying, have relatively low selectivity for Ca^{2+} over Na^+, and are activated by DAG (Hofmann et al., 1999; Okada et al., 1999; Putney et al., 2004). These channels seem to play important roles in vascular and airway smooth muscle (Corteling et al., 2004; Trebak et al., 2003; Yu et al., 2003). *N*-linked glycosylation (Dietrich et al., 2003), as well as Ca^{2+} modulation, may determine basal channel activity. Receptor-stimulated exocytosis may stimulate plasma membrane insertion of TRPC3 and C6 channels to contribute to receptor stimulation of Ca^{2+} influx (Cayouette et al., 2004; Singh et al., 2004). TRPC3 can assemble with TRPC1/4/5 in the embryonic brain (Strübing et al., 2003). TRPC3 channels can be directly phosphorylated by protein kinase G (Kwan et al., 2004) and TRPC6 by tyrosine phosphorylation by Src family protein tyrosine kinases (Hisatsune et al., 2004). In the mammalian brain, TRPC3 is activated through a pathway that is initiated by binding of brain-derived nerve factor to TrkB and engagement of a PLCγ and the IP_3 receptor (Li et al., 1999). TRPC6 and 7 channels are regulated by Ca^{2+} through differential Ca^{2+}/calmodulin-dependent and -independent mechanisms (Shi et al., 2004).

The TRPV Channels

The TRPV channel subfamily has six members divided into two groups: V1/V2/V3/V4 and V5/V6. The vanilloid receptor, TRPV1, is the best understood ion channel in this class (Caterina et al., 1997; Caterina and Julius, 2001).

The expressed TRPV1 capsaicin receptor is a heat/proton/lipid/voltage-modulated Ca^{2+}-permeant (P_{Ca}/P_{Na} ~10) ion channel (Caterina and Julius, 2001). A more voltage-gating-centric explanation is that at warmer temperatures (>37°C) or in the presence of capsaicin, TRPV1 current is activated by a more physiological range of voltages (Brauchi et al., 2004; Voets et al., 2004). TRPV1 is desensitized by internal Ca^{2+}; it is not activated by store depletion. TRPV1, V2, and V3 are activated by the synthetic compound, 2-aminoethoxydiphenylborate (2-APB) (Chung et al., 2004b; Hu et al., 2004). Endogenous cannabinoid receptor ligands, such as anandamide, are potential TRPV1 agonists. The size of its current is increased by acid pH and is modulated by intracellular PIP_2, which inhibits the channel (Chuang et al., 2001). Experiments using TRPV1 knockout mice confirm that it is essential for transducing the nociceptive, inflammatory, and hypothermic effects of vanilloid compounds and contributes to acute thermal nociception and thermal hyperalgesia following tissue injury (Caterina et al., 2000; Davis et al., 2000). However, one group proposed that intact nociceptors in vivo lacking TRPV1 and TRPV2 have normal heat responses (Woodbury et al., 2004). TRPV1 current is potentiated by bradykinin and nerve growth factor via several possible mechanisms, including PLC-mediated protein kinase C (PKC) activation and/or PIP_2 hydrolysis and phosphatidylinositol 3-kinase (Premkumar and Ahern, 2000; Chuang et al., 2001; Zhuang et al., 2004). In afferent nerve terminals and within the epithelial cells that line the bladder lumen, TRPV1 is essential for normal mechanically evoked purinergic signaling by the urothelium (Birder et al., 2002). TRPV1 also has proposed far-reaching functions ranging from satiety (Ahern, 2003) to hearing modulation (Zheng et al., 2003).

The vanilloid receptor-like channel, TRPV2, is 50% identical to TRPV1, but is insensitive to capsaicin (Caterina et al., 1999). Like TRPV1 it is more permeable to Ca^{2+} than to Na^+ (P_{Ca}/P_{Na} = 3:1). It has been proposed to mediate high-threshold noxious heat sensation, perhaps in the lightly myelinated Aδ nociceptors, but its presence in nonsensory tissue suggests other functions as well. TRPV2 is immunolocalized to hypothalamic paraventricular, suprachiasmatic, and supraoptic nuclei, preferentially in oxytocinergic and vasopressinergic neurons (Wainwright et al., 2004), and in myenteric plexus and nodose ganglion afferent neurons (Kashiba et al., 2004). TRPV2 in mouse vascular myocytes may function as a stretch sensor in vascular smooth muscle (Muraki et al., 2003) and be downstream of protein kinase A activation in mast cells (Stokes et al., 2004).

TRPV3 is expressed widely but most strikingly in skin. Increasing temperature from 22 to 40°C in mammalian cells transfected with hTRPV3 elevates intracellular calcium by activating a nonselective cationic conductance (P_{Ca}/P_{Na} ~10:1) (Peier et al., 2002b; Smith et al., 2002; Xu et al., 2002). As in sensory neurons, the current is steeply dependent on temperature, sensitizes with repeated heating, and displays a striking hysteresis on heating and cooling (Xu et al., 2002), but the extent of expression in sensory neurons is controversial. Based on these properties, TRPV3 is thermosensitive in the physiological range of temperatures between TRPM8 and TRPV1 and may play a role in pain. Primary keratinocytes isolated from mouse skin exhibit heat-evoked TRPV3 currents to mild increases in temperature (Chung et al., 2004a).

TRPV4 is ~40% identical to TRPV1 and TRPV2 (Liedtke et al., 2000; Strotmann et al., 2000). When expressed in mammalian cells it comprises a moderately selective cation channel (P_{Ca}/P_{Na} = 6), which, like TRPV1, displays a gently outwardly rectifying I–V relation. In isotonic media, TRPV4 is active, but the current is further increased by reduction of extracellular osmolality (cell swelling), with 50% activation by 270 mOsmol/l (physiological = 290 mOsmol/l). Hypertonic media (cell shrinking) decreased current activation. Deletion of the ankyrin repeat domains blunted the response to low osmolar solutions (Liedtke et al., 2000). Store depletion did not activate the channel. Anandamide and its metabolite arachidonic acid activate TRPV4 indirectly via the cytochrome P450 epoxygenase-dependent formation of epoxyeicosatrienoic acids (Watanabe et al., 2003). Experiments with TRPV4−/− mice have given somewhat conflicting results in serum osmolar regulation by the central nervous system (Liedtke et al., 2003; Mizuno et al., 2003). TRPV4 may function as an osmo-transducer in primary afferent nociceptive nerve fibers (Alessandri-Haber et al., 2003), in water-impermeant nephron segments (Tian et al., 2004), and in human airway smooth muscle cells (Jia et al., 2004). Primary keratinocytes isolated from mouse skin exhibit strong heat-evoked TRPV4 currents to mild increases in temperature (Chung et al., 2004a). *Trpv4*−/− mice have reduced sensitivity to pressure and acidic nociception (Suzuki et al., 2003) and reduced heat hyperalgesia (Tominaga and Caterina, 2004).

TRPV5 and TRPV6 comprise a separate subfamily of TRPVs with only ~30% identity with TRPV1. The expressed channels strongly inwardly rectify and are the most Ca^{2+}-selective (P_{Ca}/P_{Na} >100) (Nilius et al., 2000; Vennekens et al., 2000; Yue et al., 2001) of all TRP channels. These properties are consistent with proposed mechanisms for Ca^{2+}-selective channels in which negatively charged glutamic or aspartic acid residues provide a binding site for divalents within the pore. Intra- and extracellular [Ca^{2+}] (Yue et al., 2001; Bödding and Flockerzi, 2004) and calmodulin (Lambers et al., 2004) regulate TRPV6 activity. The localization of TRPV5 and TRPV6 to the proximal small intestine and collecting duct of the kidney, along with mouse knockout data, suggests that this family is important in calcium uptake via epithelial cells (Hoenderop et al., 2005). TRPV5−/−

mice have diminished renal Ca^{2+} reabsorption despite enhanced vitamin D levels, resulting in hypercalciuria (Hoenderop and Bindels, 2005). Like several other TRP channels, TRPV6 has been linked to cancer progression and TRPV6 has been used as a prognostic marker for prostate cancer (Fixemer et al., 2003).

The TRPM Channels

The TRPM subfamily has eight members divided into four groups: M1 (melastatin)/M3, M7 (TRP-PLIK)/M6, M2/M8, and M4/M5. Down-regulation of the 1533aa TRPM1 protein in the primary cutaneous tumor is a prognostic marker for metastasis in patients with localized melanoma (Duncan et al., 1998; Hunter et al., 1998). TRPM1 may be regulated through direct interaction with a cytosolic isoform generated by alternative RNA splicing (Xu et al., 2001), but TRPM1 ion currents have not been measured. The *Caenorhabditis elegans gon-2* gene, a homolog of TRPM1, is required for postembryonic mitotic cell division of gonadal precursor cells (West et al., 2001). MITF, an essential transcription factor for melanocyte development, is an important transcriptional regulator of TRPM1 (Miller et al., 2004).

TRPM2 is a 1503aa protein that is highly expressed in brain (Nagamine et al., 1998) and present in blood cells. The channel is nonselective and displays a linear I–V relation. A NUDT9 Nudix hydrolase family domain within the TRPM2 sequence suggests that the channel may be regulated by nucleoside diphosphates, and current is increased when HEK-293 cells expressing TRPM2 are perfused with adenosine diphosphoribose or βNAD (Perraud et al., 2001; Sano et al., 2001). In addition, the C-terminal NUDT9 domain confers adenosine diphosphoribose hydrolase activity. The channel is regulated by signaling pathways responsive to H_2O_2 and tumor necrosis factor-α, suggesting that its physiological role may be as a sensor of redox status in cells (Hara et al., 2002; Wehage et al., 2002; Perraud et al., 2003).

Identified first by sequencing projects, the function of TRPM3 is poorly understood. The hTRPM3 gene maps to human chromosome 9q-21.12 and encodes a 1555-amino acid protein. Expressed primarily in kidney and, at lesser levels, in brain, testis, and spinal cord, hTRPM3 is nonselective (P_{Ca}/P_{Na} ~1.6). Hypotonicity reportedly increases calcium entry in TRPM3-expressing HEK293 cells (Grimm et al., 2003; Lee et al., 2003). D-*erythro*-Sphingosine, a metabolite in synthesis of cellular sphingolipids, but not sphingosine-1-phosphate and ceramide, activates TRPM3 (Grimm et al., 2004).

TRPM4 and TRPM5 have similar characteristics. TRPM4b, a splice variant of TRPM4, and TRPM5 are Ca^{2+}-activated, voltage-modulated, monovalent-selective cation channels with ~25 pS single-channel conductances (Launay et al., 2002; Hofmann et al., 2003; Nilius et al., 2003). Sustained increased $[Ca^{2+}]_i$ desensitizes TRPM5 channels, but PIP_2 partially restores channel activity (Liu and Liman, 2003). TRPM4/TRPM5-dependent currents contribute to myogenic vasoconstriction of cerebral arteries (Earley et al., 2004), and TRPM5 is important in taste (sweet, bitter, and umami) transduction (Perez et al., 2002; Zhang et al., 2003b). TRPM4b-mediated depolarization modulates intracellular calcium oscillations in T lymphocytes, with downstream effects on cytokine production (Zhang et al., 2003a; Launay et al., 2004). Decavanadate modulates TRPM4, but not TRPM5, apparently via a C-terminal positively charged domain (homologous to a site on SERCA pumps), by inhibiting voltage-dependent closure of the channel (Nilius et al., 2004).

TRPM6 and TRPM7 comprise a unique subfamily of TRP proteins with both channel and kinase activities. TRPM7, which has 1863 amino acid residues, was identified in a yeast two-hybrid screen as a protein interacting with PLCβ_1 (Runnels et al., 2001). It seems to be ubiquitously expressed. The structure of the C-terminal kinase domain has been determined (Yamaguchi et al., 2001), and annexin 1 is one potential substrate (Dorovkov and Ryazanov, 2004). Although the kinase domain for TRPM7 has little sequence similarity to conventional protein kinases, its structure resembles that of many eukaryotic protein kinases (e.g., cAMP-dependent protein kinase) with the notable exception of having its own zinc-finger domain. TRPM7 exhibits a steeply outwardly rectifying conductance when expressed in mammalian cells (P_{Ca}/P_{Na} = 3:1), passing very little inward current. TRPM7 is inhibited by intracellular magnesium (0.3–1.0 mM range) (Nadler et al., 2001). Although the mechanism of activation of TRPM6/7 is unknown, receptor-mediated activation of PLC by hormones or growth factors inhibits channel activity by hydrolyzing and reducing local PIP_2 concentrations (Runnels et al., 2002). TRPM7 has been proposed to underlie the majority of cell deaths during prolonged anoxia in brain (Aarts et al., 2003). TRPM6 is the longest member (2011aa) of the TRP channel family and may form heteromeric channels with TRPM7. TRPM6 mutations in humans result in hypomagnesemia with secondary hypocalcemia (Schlingmann et al., 2002; Walder et al., 2002). Coupled with their permeation by Mg^{2+} (Nadler et al., 2001), this has led to the proposal that TRPM6 and M7 play a major role in Mg^{2+} homeostasis (Wolf, 2004).

TRPM8 is a 1104aa protein that does not seem to contain associated enzymatic domains. TRPM8 is a nonselective, voltage-modulated conductance. At colder temperatures (8–28°C) or in the presence of menthol, TRPM8 current is activated at a more physiological range of voltages (Brauchi et al., 2004; Voets et al., 2004). This channel is expressed in small-diameter primary sensory neurons, where it presumably functions as a thermosensor (McKemy et al., 2002; Peier et al., 2002a). TRPM8 is also expressed in prostate epithelium (Tsavaler et al., 2001), where it is proposed to be an androgen responsive channel (Zhang and Barritt, 2004).

The TRPA Channel

TRPA1 is the most distinct of the four central (TRPC, V, M, and A) subclasses, with no known related family members, and contains more than a dozen ankyrin repeats in its N terminus. It was originally proposed to sense painfully cold temperatures (Story et al., 2003), but a more conservative description is that it is sensitive to membrane/cytoskeletal perturbations by cold, plant compounds such as mustard oils (Bandell et al., 2004; Jordt et al., 2004), and perhaps stretch [as the hearing transduction channel (Corey et al., 2004)]. TRPA1 is expressed in sensory neurons of dorsal root and trigeminal ganglia and the ear and, based on transcripts, is fairly widely expressed. TRPA1 is also activated downstream of G protein-coupled receptors that stimulate PLC and may depolarize nociceptors in response to proalgesic agents such as bradykinin, histamine, serotonin, or ATP. TRPA1 is expressed in trigeminal and dorsal root ganglia and the ear.

The TRPP Proteins

Polycystic kidney disease (PKD) proteins, or polycystins PKD2 (TRPP1), PKD2L1 (TRPP2), and PKD2L2 (TRPP3) comprise the 6TM Ca^{2+}-permeant channels (Delmas, 2004). The much larger polycystin-1 (PKD1), polycystin-REJ, and polycystin-1L1 proteins are 11TM proteins that contain a C-terminal 6TM TRP-like channel domain. Polycystin1 is not known to form a channel by itself, but such a possibility has been raised by one recent study (Babich et al., 2004). According to another report, it complexes with TRPP2 to form a Ca^{2+}-permeable nonselective cation channel with a linear I–V relation (Hanaoka et al., 2000). Autosomal dominant polycystic kidney disease is caused by mutations in polycystin-1 or TRPP1, leading to alterations in polarization and function of cyst-lining epithelial cells. Polycystin-1−/− and Trpp1−/− mice die in utero with cardiac septal defects and cystic changes in nephrons and pancreatic ducts (Wu et al., 1998). The mouse ortholog of TRPP2 is deleted in *krd* mice, resulting in defects in kidney and retina (Nomura et al., 1998; Pennekamp et al., 2002). Motile monocilia generate nodal flow and nonmotile TRPP1-containing cilia sense nodal flow, initiating an asymmetric Ca^{2+} signal at the left nodal border (Nonaka et al., 2002). Polycystin-1 and TRPP1 both seem to be targeted to primary cilia cells of renal epithelia, where the channel complex is gated by fluid flow (Nauli et al., 2003).

The TRPML Proteins

The mucolipins (TRPML1, 2, and 3; MCOLN1, 2, and 3) are 6TM channels that are probably restricted to intracellular vesicles (Bach, 2004). Mutations in MCOLN1 (TRPML1) are associated with mucolipidosis type IV, a neurodegenerative lysosomal storage disorder (Sun et al., 2000; Bach, 2001; Slaugenhaupt, 2002). The defect seems to be in sorting or transport in the late endocytic pathway. Mutations in a *C. elegans* TRPML1 homolog, *cup-5,* cause excess lysosome formation and apoptosis in all cell types (Hersh et al., 2002; Treusch et al., 2004). TRPML3 is present in the cytoplasm of hair cells and the plasma membrane of sterocilia. TRPML3 is mutated in the *varitint-waddler* mouse, resulting in deafness and pigmentation defects (Di Palma et al., 2002).

Summary

The TRP channels are a family of ion channel proteins that permeate Na^+ and Ca^{2+} and, in several cases, Mg^{2+}. Most cells contain several to many TRP subunits, complicating the separation of monomeric and heteromeric channel characteristics. The multipotent phosphatidylinositol pathway is involved in most TRP channel regulation, but the details of this regulation are just beginning to be elucidated. At this time there is no unifying theme in their mechanism for activation.

Since TRPs are intimately linked with intracellular Ca^{2+} signaling, they are implicated in the control of cell cycle progression, cell migration, and programmed cell death. TRP channels also seem to be important in epithelial uptake of divalent ions. Genetic approaches combined with robust assays have most clearly established their roles in sensory functions. Tables 1 through 28 summarize the molecular, physiological, and pharmacological properties of these ion channels in more detail.

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TABLE 1
TRPC1 channel

Channel name	TRPC1[1–8]
Description	Nonselective cation channel subunit
Other names	TRP1
Molecular information	Human unigene: Hs0.250687, chr. 3q22–3q24 Mouse unigene: Mm0.149633
Associated subunits	TRPC4, TRPC5 (TRPC3–embryo), calmodulin, IP_3Rs, caveolin-1, Gq/11, PMCA, mGluR1
Functional assays	Patch-clamp, calcium imaging
Current	Outwardly rectifying when coexpressed with TRPC4 and TRPC5
Conductance	Not established
Ion selectivity	P_{Na}/P_{Ca} ~1:1 (when coexpressed with TRPC4 and TRPC5)[5]
Activation	Stretch?
Inactivation	Not established
Activators	Recording of G_q-coupled receptor (heteromer TRPC1/TRPC5), whole cell current, augmented store-operated influx as presumed homomer; no direct agonists identified, gated in response to stimulation of the G_q-coupled receptors, augmented by La^{3+} (heteromer of TRPC1 with TRPC4 or TRPC5)[5]; it has been proposed that the mGluR1-evoked slow EPSC is mediated by the TRPC1 cation channel; TRPC1 is expressed in perisynaptic regions of the cerebellar parallel fiber-Purkinje cell synapse and may be physically associated with mGluR1[6]
Gating inhibitors	None
Blockers	Inhibited by 80 μM 2-APB (heteromer) and Gd^{3+}
Radioligands	None
Channel distribution	Widely expressed; highest levels in brain, heart, kidney, lung, skeletal muscle, prostate, skin testis, ovaries
Physiological functions	Putative role in receptor-mediated, Ca^{2+}-dependent secretion and contraction
Mutations and pathophysiology	Not established
Pharmacological significance	Involved in Ca^{2+} entry induced by phospholipid hydrolysis (PI response) and Ca^{2+} store depletion
Comments	Splice variants in human and mouse

chr., chromosome; PMCA, plasma membrane calcium pump; EPSC, excitatory postsynaptic current; PI, phosphatidylinositol.

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TABLE 2
TRPC2 channel

Channel name	TRPC2[1–7]
Description	Mouse pheromone channel
Other names	mTrp2 (in mouse)
Molecular information	Human unigene: Hs0.131910 probable pseudogene, chr. 0.7 Mouse unigene: Mm0.292904, chr. 11p15.4-p15.3
Associated subunits	Not established
Functional assays	Patch-clamp
Current	Near linear, nonselective cation conductance
Conductance	42pS (symmetrical 140 Na^+)[7]
Ion selectivity	Cation nonselective
Activation	Indirect via pheromone receptors
Inactivation	Not established
Activators	DAGs (10–100 μM)
Gating inhibitors	None
Blockers	None
Radioligands	None
Channel distribution	Vomeronasal organ, testis, heart, kidney, brain, sperm
Physiological functions	Sensory transduction in vomeronasal organ, possible role in acrosome reaction in sperm
Mutations and pathophysiology	TRPC2-deficient mice display abnormal mating behavior
Pharmacological significance	Candidate for mammalian pheromone sensory signaling
Comments	Human and bovine versions are likely to be pseudogenes[2]; the murine channel is expressed as multiple splice variants

chr., chromosome.

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TABLE 3
TRPC3 channel

Channel name	TRPC3[1–6]
Description	Diacylglycerol-Ca^{2+}-activated TRP channel
Other names	mTRPC3
Molecular information	Human unigene: Hs0.150981, chr. 4q27 Mouse unigene: Mm0.74363, chr. 3
Associated subunits	TRPC6, TRPC7, FKBP12, VAMP2, syntaxin, SNAP, NCX1, TrkB
Functional assays	Patch-clamp, calcium imaging
Current	Inwardly and outwardly rectifying, nonselective cation current
Conductance	66pS[2]
Ion selectivity	P_{Na}/P_{Ca} = 1:1.5
Activation	Intracellular Ca^{2+}
Inactivation	Not established
Activators	Activated either by DAG or direct interaction with the IP_3 receptor in vitro; activated through a BDNF, TrkB-mediated pathway in neurons
Gating inhibitors	None
Blockers	2-APB, 1–25 μM Gd^{3+}, La^{3+}, RuR
Radioligands	None
Channel distribution	Brain, placenta, heart, muscle, smooth muscle
Physiological functions	Resistance artery myogenic tone, airway regulation
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	DAG response is PKC-independent

chr., chromosome; TrkB, tyrosine kinase B; BDNF, brain-derived neurotrophic factor; RuR, ruthenium red.

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TABLE 4
TRPC4 channel

Channel name	TRPC4[1–8]
Description	TRP receptor-operated channel
Other names	TRP4, CCE1, bCCE
Molecular information	Human unigene: Hs0.262960, chr. 13q13.1-q13.2 Mouse unigene: Mm0.10100, chr. 3
Associated subunits	Forms homomeric channels in mouse; TRPC1, TRPC5
Functional assays	Patch-clamp, calcium imaging
Current	Nonselective, largely inward, double rectification
Conductance	41pS; unclear as homomer; estimates range from 18 to 40pS
Ion selectivity	P_{Na}/P_{Ca} = 1:1.1,[2] 1:7[3]
Activation	Activation of G_q-coupled receptors is known to activate TRPC4 current through activation of PLCβ
Inactivation	Not established
Activators	La^{3+} (100 μM) augments current
Gating inhibitors	None
Blockers	2-APB, mM La^{3+}, niflumic acid
Radioligands	None
Channel distribution	Brain, testis, placenta, adrenal gland, endothelium
Physiological functions	Mediates agonist-dependent vasorelaxation in vascular endothelium
Mutations and pathophysiology	Impaired agonist-dependent vasorelaxation in TRPC4 −/− mice
Pharmacological significance	Possibly involved in signaling complexes
Comments	Coexpression with TRPC1 or TRPC5 results in a novel NMDA-like voltage-dependent channel

chr., chromosome; NMDA, *N*-methyl-D-aspartate.

1. Okada T, Shimizu S, Wakamori M, Maeda A, Kurosaki T, Takada N, Imoto K, and Mori Y (1998) Molecular cloning and functional characterization of a novel receptor-activated TRP Ca^{2+} channel from mouse brain. *J Biol Chem* **273:**10279–10287.

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TABLE 5
TRPC5 channel

Channel name	TRPC5[1–7]
Description	TRP receptor-operated channel
Other names	TRP5, CCE2
Molecular information	Human unigene: Hs0.247868, chr. Xq23 Mouse unigene: Mm0.328378, chr. X
Associated subunits	Forms heteromultimers with TRPC1 and TRPC4
Functional assays	Patch-clamp, calcium imaging
Current	Nonselective, double rectification
Conductance	~38pS as homomer, ~5pS as TRPC1/C5 heteromer
Ion selectivity	P_{Na}/P_{Ca} = 1:9,[1] 1:1.8[2]
Activation	Stimulation of G_q-coupled receptors, receptor tyrosine kinases
Inactivation	Not established
Activators	Activation of G_q-coupled receptors is known to activate TRPC5 current through activation of PLCγ; La^{3+} (100 μM) augments current
Gating inhibitors	None
Blockers	mM La^{3+}, 2-APB
Radioligands	None
Channel distribution	Brain, lung, placenta, testis
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	Channel properties of heteromeric TRPC1/TRPC4 or TRPC1/TRPC5 are distinct from those of TRPC4 or TPRC5 homomers; rapid insertion of vesicles in growth cones; regulator of neurite morphology

chr., chromosome; RTK, receptor tyrosine kinase.

1. Okada T, Shimizu S, Wakamori M, Maeda A, Kurosaki T, Takada N, Imoto K, and Mori Y (1998) Molecular cloning and functional characterization of a novel receptor-activated TRP Ca^{2+} channel from mouse brain. *J Biol Chem* **273:**10279–10287.

2. Schaefer M, Plant TD, Obukhov AG, Hofmann T, Gudermann T, and Schultz G (2000) Receptor-mediated regulation of the nonselective cation channels TRPC4 and TRPC5. *J Biol Chem* **275:**17517–17526.

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TABLE 6
TRPC6 channel

Channel name	TRPC6[1–7]
Description	DAG-activated channel
Other names	None
Molecular information	Human unigene: Hs0.159003, chr. 11q21-q22 Mouse unigene: Mm0.325086, chr. 9
Associated subunits	TRPC3, TRPC7, calmodulin, FKBP12
Functional assays	Patch-clamp, calcium imaging
Current	Inwardly and outwardly rectifying, nonselective cation current
Conductance	35pS (symmetrical 120 Cs^+)
Ion selectivity	P_{Na}/P_{Ca} ~1:5
Activation	Sensitive to intracellular Ca^{2+}
Inactivation	Not established
Activators	DAGs
Gating inhibitors	None
Blockers	0.25 mM Cd^{2+}, 4 μM La^{3+}, 2 μM Gd^{2+}, 130 μM amiloride, 4 μM SKF96365, 100 μM 2-APB
Radioligands	None
Channel distribution	Lung, heart, brain, muscle
Physiological functions	Cation influx in response to DAG generated by receptor-mediated activation of PLCβ and PLCγ
Mutations and pathophysiology	Not established
Pharmacological	Candidate for receptor-stimulated currents in smooth muscle significance cells
Comments	The DAG response is PKC-independent

chr., chromosome.

1. Hofmann T, Obukhov AG, Schaefer M, Harteneck C, Gudermann T, and Schultz G (1999) Direct activation of human TRPC6 and TRPC3 channels by diacylglycerol. *Nature (Lond)* **397:**259–263.

2. Okada T, Inoue R, Yamazaki K, Maeda A, Kurosaki T, Yamakuni T, Tanaka I, Shimizu S, Ikenaka K, Imoto K, et al. (1999) Molecular and functional characterization of a novel mouse transient receptor potential protein homologue TRP7. Ca^{2+}-permeable cation channel that is constitutively activated and enhanced by stimulation of G protein-coupled receptor. *J Biol Chem* **274:**27359–27370.

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7. Shi J, Mori E, Mori Y, Mori M, Li J, Ito Y, and Inoue R (2004) Multiple regulation by calcium of murine homologues of transient receptor potential proteins TRPC6 and TRPC7 expressed in HEK293 cell. *J Physiol* **561:**415–432.

TABLE 7
TRPC7 channel

Channel name	TRPC7[1,2]
Description	Cardiac TRP channel
Other names	TRP7
Molecular information	Human unigene: Hs0.283104, chr. 5q31.1 Mouse unigene: Mm0.62409, chr. 13 B2
Associated subunits	TRPC3, TRPC6, calmodulin, FKBP12
Functional assays	Patch-clamp, calcium imaging
Current	Inwardly and outwardly rectifying, nonselective cation current
Conductance	50pS (0–100 mV); 25pS (−100 to 0 mV)
Ion selectivity	P_{Na}/P_{Ca} ~1:1.9
Activation	Sensitive to intracellular Ca^{2+}
Inactivation	Not established
Activators	DAG and analogs (100 μM)
Gating inhibitors	None
Blockers	La^{3+} (100 μM), SKF96365 (25 μM), 0.1–0.4 mM $[Ca^{2+}]_o$
Radioligands	None
Channel distribution	Heart, lung, eye, brain, spleen, testis
Physiological functions	Cation influx in response to G_q activation
Mutations and pathophysiology	Not established
Pharmacological significance	Extracellular ATP (possibly via purinergic receptors), modulated by intracellular calcium, PKC

chr., chromosome.

1. Okada T, Inoue R, Yamazaki K, Maeda A, Kurosaki T, Yamakuni T, Tanaka I, Shimizu S, Ikenaka K, Imoto K, et al. (1999) Molecular and functional characterization of a novel mouse transient receptor potential protein homologue TRP7. Ca^{2+}-permeable cation channel that is constitutively activated and enhanced by stimulation of G protein-coupled receptor. *J Biol Chem* **274:**27359–27370.

2. Shi J, Mori E, Mori Y, Mori M, Li J, Ito Y, and Inoue R (2004) Multiple regulation by calcium of murine homologues of transient receptor potential proteins TRPC6 and TRPC7 expressed in HEK293 cell. *J Physiol* **561:**415–432.

TABLE 8
TRPV1 channel

Channel name	TRPV1[1–8]
Description	Vanilloid (capsaicin) receptor and noxious thermosensor
Other names	VR1, OTRPC1
Molecular information	Human unigene: Hs0.268606, chr. 17p13.3 Mouse unigene: Mm0.278432, chr. 11 B3
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging, knockout mouse
Current	Outwardly rectifying nonselective current
Conductance	83pS for heat, 77pS for capsaicin activation measured at positive potentials; E_{rev} in saline solution $\sim$ 0 mV
Ion selectivity	P_{Na}/P_{Ca} = 1:9 for capsaicin-activated current, permeability $Ca^{2+} > Mg^{2+} > Na^{+} \sim K^{+} \sim Cs^{+}$ P_{Na}/P_{Ca} = 1:4 for heat-activated current
Activation	Increasing temperature shifts voltage activation to the physiological range of voltages
Inactivation	cAMP-dependent protein kinase directly phosphorylates TRPV1 to regulate desensitization
Activators	Capsaicin (EC_{50} = 0.7 μM), resiniferatoxin (EC_{50} = 40 nM), anandamide, heat (threshold ~43°C), extracellular protons (indirect sensitization by bradykinin, NGF), ethanol
Blockers	Capsazepine, ruthenium red, iodo-resiniferatoxin, BCTC, PIP_2
Gating inhibitors	None
Radioligands	[^{3}H]Resiniferatoxin
Channel distribution	Mainly in trigeminal and dorsal root ganglia, also brain, spinal cord
Physiological functions	Depolarization and calcium entry in response to heat or endogenous agonist, exogenous capsaicin, pain sensation, vasodilation by anandamide
Mutations and pathophysiology	Required for inflammatory thermal hyperalgesia; capsaicin binding site has been determined
Pharmacological significance	Potential target for pain-relieving agents
Comments	TRPV1 is not activated by store depletion

chr., chromosome; NGF, nerve growth factor.

1. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, and Julius D (1997) The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature (Lond)* **389:**816–824.

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TABLE 9
TRPV2 channel

Channel name	TRPV2[1–6]
Description	Noxious heat thermosensor channel
Other names	VRL-1, GRC, OTRPC2
Molecular information	Human unigene: Hs0.279746, chr. 17p11.2 Mouse unigene: Mm0.288064, chr. 11 B2
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging
Current	Outwardly rectifying nonselective cation current
Conductance	E_{rev} in saline solution ~0 mV
Ion selectivity	P_{Na}/P_{Ca} = 1:3 $Ca^{2+} > Mg^{2+} > Na^{+}$, K^{+}, Cs^{+}
Activation	High temperature (>52°C), PKA modulation of surface expression
Inactivation	Not established
Activators	Heat (threshold = 52°C), IGF-I
Gating inhibitors	None
Blockers	Ruthenium red, La^{3+}, SKF96365
Radioligands	None
Channel distribution	Mainly dorsal root ganglion neurons, brain, spinal cord, spleen, and lung
Physiological functions	Calcium entry in thermal pain sensation
Mutations and pathophysiology	Not established
Pharmacological significance	Potential target for pain-relieving agents
Comments	Insensitive to capsaicin

chr., chromosome; PKA, protein kinase A; IGF-I, insulin-like growth factor-I.

1. Caterina MJ, Rosen TA, Tominaga M, Brake AJ, and Julius D (1999) A capsaicin-receptor homologue with a high threshold for noxious heat. *Nature (Lond)* **398:**436–441.
2. Hu HZ, Gu Q, Wang C, Colton CK, Tang J, Kinoshita-Kawada M, Lee LY, Wood JD, and Zhu MX (2004) 2-Aminoethoxydiphenyl borate is a common activator of TRPV1, TRPV2 and TRPV3. *J Biol Chem* **279:**35741–35748.
3. Muraki K, Iwata Y, Katanosaka Y, Ito T, Ohya S, Shigekawa M, and Imaizumi Y (2003) TRPV2 is a component of osmotically sensitive cation channels in murine aortic myocytes. *Circ Res* **93:**829–838.
4. Stokes AJ, Shimoda LM, Koblan-Huberson M, Adra CN, and Turner H (2004) A TRPV2-PKA signaling module for transduction of physical stimuli in mast cells. *J Exp Med* **200:**137–147.
5. Woodbury CJ, Zwick M, Wang S, Lawson JJ, Caterina MJ, Koltzenburg M, Albers KM, Koerber HR, and Davis BM (2004) Nociceptors lacking TRPV1 and TRPV2 have normal heat responses. *J Neurosci* **24:**6410–6415.
6. Stokes AJ, Wakano C, Del Carmen KA, Koblan-Huberson M, and Turner HJ (2005) Formation of a physiological complex between TRPV2 and RGA protein promotes cell surface expression of TRPV2. *J Cell Biochem* **94:**669–683.

TABLE 10
TRPV3 channel

Channel name	TRPV3[1–5]
Description	Warmth sensor channel
Other names	None
Molecular information	Human unigene: Hs0.446255, chr. 17p13.2 Mouse unigene: Mm0.347652, chr. 11 B4
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging
Current	Outwardly rectifying nonselective cation current
Conductance	170pS
Ion selectivity	P_{Na}/P_{Ca} = 0.08
Activation	~35°C
Inactivation	Cooling
Activators	Increasing temperature
Gating inhibitors	None
Blockers	Ruthenium red
Radioligands	None
Channel distribution	Brain (cortex, thalamus), skin, hair follicles, tongue, stomach, spinal cord, superior cervical ganglion, dorsal root ganglion, trigeminal ganglion
Physiological functions	Putative, warm sensation
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	Like TRPV1 and TRPV2, TRPV3 exhibits sensitivity to temperature changes; unique features are hysteresis behavior on heating and cooling and sensitization

chr., chromosome.

1. Peier AM, Reeve AJ, Andersson DA, Moqrich A, Earley TJ, Hergarden AC, Story GM, Colley S, Hogenesch JB, McIntyre P, Bevan S, and Patapoutian A (2002) A heat-sensitive TRP channel expressed in keratinocytes. *Science (Wash DC)* **296:**2046–2049.
2. Xu H, Ramsey, I. Kotecha SA, Moran, M. Chong JA, Lawson D, Ge P, Lilly J, Silos-Santiago I, Xie Y, et al. (2002) TRPV3 is a calcium-permeable temperature-sensitive cation channel. *Nature (Lond)* **418:**181–186.
3. Smith GD, Gunthorpe MJ, Kelsell RE, Hayes PD, Reilly P, Facer P, Wright JE, Jerman JC, Walhin JP, Ooi L, et al. (2002) TRPV3 is a temperature-sensitive vanilloid receptor-like protein. *Nature (Lond)* **418:**186–190.
4. Chung MK, Lee H, Mizuno A, Suzuki M, and Caterina M (2004a) TRPV3 and TRPV4 mediate warmth-evoked currents in primary mouse keratinocytes. *J Biol Chem* **279:**21569–21575.
6. Hu HZ, Gu Q, Wang C, Colton CK, Tang J, Kinoshita-Kawada M, Lee LY, Wood JD, and Zhu MX (2004) 2-Aminoethoxydiphenyl borate is a common activator of TRPV1, TRPV2 and TRPV3. *J Biol Chem* **279:**35741–35748.

TABLE 11
TRPV4 channel

Channel name	TRPV4[1–11]
Description	Osmosensor channel
Other names	OTRPC4, VR-OAC, VRL-2, TRP-12
Molecular information	Human unigene: Hs0.506713, chr. 12q24.1 Mouse unigene: Mm0.266450, chr. 5
Associated subunits	Calmodulin
Functional assays	Patch-clamp, calcium imaging
Current	Outwardly rectifying, nonselective current
Conductance	90pS
Ion selectivity	P_{Na}/P_{Ca} = 1:6
Activation	Osmolarity (EC_{50} = 270 mOsmol/l), phorbol esters, arachidonic acid, EETs, stretch
Inactivation	Calmodulin/Ca^{2+}
Activators	Reduced osmolarity (see "Comments")
Gating inhibitors	None
Blockers	Ruthenium red, gadolinium, lanthanum
Radioligands	None
Channel distribution	Brain, liver, kidney, fat, heart, testis, salivary gland, trachea
Physiological functions	Osmolarity sensing with thermal modulation
Mutations and pathophysiology	Deletion of the ankyrin repeat domain blunts the response to low osmolarity solutions
Pharmacological significance	Not established
Comments	TRPV4 is not activated by store depletion

chr., chromosome; VR-OAC, vanilloid receptor-related osmotically activated channel; EET, eicosatetraenoic acid.

1. Strotmann R, Harteneck C, Nunnenmacher K, Schultz G, and Plant TD (2000) OTRPC4, a nonselective cation channel that confers sensitivity to extracellular osmolarity. *Nat Cell Biol* **2:**695–702.

2. Denis CS, Sali A, Hudspeth AJ, Friedman JM, and Heller S (2000) Vanilloid receptor-related osmotically activated channel (VR-OAC), a candidate vertebrate osmoreceptor. *Cell* **103:**525–535.

3. Mizuno A, Matsumoto N, Imai M, and Suzuki M (2003) Impaired osmotic sensation in mice lacking TRPV4. *Am J Physiol Cell Physiol* **285:**C96–C101.

4. Liedtke W, Tobin DM, Bargmann CI, and Friedman JM (2003) Mammalian TRPV4 (VR-OAC) directs behavioral responses to osmotic and mechanical stimuli in *Caenorhabditis elegans*. *Proc Natl Acad Sci USA* **100 (Suppl 2):**14531–14536.

5. Watanabe H, Vriens J, Prenen J, Droogmans G, Voets T, and Nilius B (2003) Anandamide and arachidonic acid use epoxyeicosatrienoic acids to activate TRPV4 channels. *Nature (Lond)* **424:**434–438.

6. Chung MK, Lee H, Mizuno A, Suzuki M, and Caterina M (2004a) TRPV3 and TRPV4 mediate warmth-evoked currents in primary mouse keratinocytes. *J Biol Chem* **279:**21569–21575.

7. Jia Y, Wang X, Varty L, Rizzo CA, Yang R, Correll CC, Phelps PT, Egan RW, and Hey JA (2004) Functional TRPV4 channels are expressed in human airway smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol* **287:**L272–L278.

8. Suzuki M, Watanabe Y, Oyama Y, Mizuno A, Kusano E, Hirao A, and Ookawara S (2003) Localization of mechanosensitive channel TRPV4 in mouse skin. *Neurosci Lett* **353:**189–192.

9. Tian W, Salanova M, Xu H, Lindsley JN, Oyama TT, Anderson S, Bachmann S, and Cohen DM (2004) Renal expression of osmotically responsive cation channel TRPV4 is restricted to water-impermeant nephron segments. *Am J Physiol Renal Physiol* **287:**F17–F24.

10. Strotmann R, Schultz G, and Plant TD (2003) Ca^{2+}-dependent potentiation of the nonselective cation channel TRPV4 is mediated by a C-terminal calmodulin binding site. *J Biol Chem*. **278:**26541–26549.

11. Vriens J, Watanabe H, Janssens A, Droogmans G, Voets T, and Nilius B (2003) Cell swelling, heat, and chemical agonists use distinct pathways for the activation of the cation channel TRPV4. *Proc Natl Acad Sci USA* **101:**396–401.

TABLE 12
TRPV5 channel

Channel name	TRPV5[1–5]
Description	Calcium-selective TRP channel
Other names	ECaC1, CaT2
Molecular information	Human unigene: Hs0.283369, chr. 7q35 Mouse unigene: Mm0.135734, chr. 6 B1
Associated subunits	NHERF, S100 protein, TRPV6
Functional assays	Patch-clamp, calcium imaging
Current	Inwardly rectifying, calcium-sensitive cation channel
Conductance	75pS in calcium-free solution E_{rev} in saline solution >50 mV
Ion selectivity	$Ca^{2+} > Ba^{2+} > Sr^{2+} > Mn^{2+}$; P_{Na}/P_{Ca} = 1:107
Activation	Mechanism not established, constitutively active
Inactivation	Not established
Activators	None
Gating inhibitors	None
Blockers	Ruthenium red (100 nM), La^{3+}
Radioligands	None
Channel distribution	Intestine, kidney, placenta
Physiological functions	Not established
Mutations and pathophysiology	D542 is crucial for calcium sensitivity
Pharmacological significance	Not established
Comments	One of only two known TRP channels (with TRPV6) that is relatively highly Ca^{2+}-selective

chr., chromosome; NHERF, Na^+/H^+ exchange regulatory factor.

1. Vennekens R, Hoenderop GJ, Prenen J, Stuiver M, Willems PHGM, Droogmans G, Nilius B, and Bindels RJM (2000) Permeation and gating properties of the novel epithelial Ca^{2+} channel. *J Biol Chem* **275:**3963–3969.

2. Nilius B, Vennekens R, Prenen J, Hoenderop JG, Bindels RJ, and Droogmans G (2000) Whole-cell and single channel monovalent cation currents through the novel rabbit epithelial Ca^{2+} channel ECaC. *J Physiol* **527 (Pt 2):**239–248.

3. Hoenderop JGJ, van der Kemp AWCM, Hartog A, van de Graaf SFJ, van Os CH, Willems PHGM, and Bindels RJM (1999) Molecular identification of the apical Ca^{2+} channel in 1,25-dihydroxyvitamin D3-responsive epithelia. *J Biol Chem* **274:**8375–8378.

4. van de Graaf SF, Hoenderop JG, Gkika D, Lamers D, Prenen J, Rescher U, Gerke V, Staub O, Nilius B, and Bindels RJ (2003) Functional expression of the epithelial Ca^{2+} channels (TRPV5 and TRPV6) requires association of the S100A10-annexin 2 complex. *EMBO J* **22:**1478–1487.

5. Embark HM, Setiawan I, Poppendieck S, van de Graaf SF, Boehmer C, Palmada M, Wieder T, Gerstberger R, Cohen P, Yun CC, et al. (2004) Regulation of the epithelial Ca^{2+} channel TRPV5 by the NHE regulating factor NHERF2 and the serum and glucocorticoid inducible kinase isoforms SGK1 and SGK3 expressed in *Xenopus* oocytes. *Cell Physiol Biochem* **14:**203–212.

TABLE 13
TRPV6 channel

Channel name	TRPV6[1–3]
Description	Calcium-selective TRP channel
Other names	ECaC2, CaT1
Molecular information	Human unigene: Hs0.302740, chr. 7q33–34 Mouse unigene: Mm0.296889, chr. 6
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging
Current	Inwardly rectifying, calcium-sensitive cation current
Conductance	42–58pS in calcium-free solution E_{rev} in saline solution >50 mV
Ion selectivity	$Ca^{2+} > Ba^{2+} > Sr^{2+} > Mn^{2+}$; P_{Na}/P_{Ca} = 1:130
Activation	Constitutively active
Inactivation	Not established
Activators	None
Gating inhibitors	None
Blockers	Ruthenium red (5 μM), La^{3+}
Radioligands	None
Channel distribution	Kidney, intestine
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	One of only two known TRP channels (with TRPV5) that is relatively highly Ca^{2+}-selective

chr., chromosome.

1. Yue L, Peng JB, Hediger MA, and Clapham DE (2001) CaT1 manifests the pore properties of the calcium-release-activated calcium channel. *Nature (Lond)* **410:**705–709.

2. Bodding M and Flockerzi V (2004) Ca^{2+} dependence of the Ca^{2+}-selective TRPV6 channel. *J Biol Chem* **279:**36546–36552.

3. Lambers TT, Weidema AF, Nilius B, Hoenderop JG, and Bindels RJ (2004) Regulation of the mouse epithelial Ca^{2+} channel TRPV6 by the Ca^{2+}-sensor calmodulin. *J Biol Chem* **279:**28855–28861.

TABLE 14
TRPM1 channel

Channel name	TRPM1[1–4]
Description	Putative melastatin TRP channel
Other names	Melastatin, LTRPC1
Molecular information	Human unigene: Hs0.155942, chr. 15q13-q14 Mouse unigene: Mm0.38875, chr. 7
Associated subunits	Short transcript of M1 (MLSN-S)
Functional assays	Calcium imaging
Current	Not established
Conductance	Not established
Ion selectivity	Ca^{2+} permeable
Activation	Not established
Inactivation	Not established
Activators	None
Blockers	None
Gating inhibitors	None
Radioligands	None
Channel distribution	Eye, melanocytes
Physiological functions	Not established
Mutations and pathophysiology	Down-regulated in melanoma
Pharmacological significance	Alternatively spliced form suppresses calcium entry though HEK cells expressing full-length melastatin
Comments	TRPM1 is the founding member of the TRPM family; alternatively spliced long and short forms exist; the two forms interact

chr., chromosome; HEK, human embryonic kidney.

1. Hunter JJ, Shao J, Smutko JS, Dussault BJ, Nagle DL, Woolf EA, Holmgren LM, Moore KJ, and Shyjan AW (1998) Chromosomal localization and genomic characterization of the mouse melastatin gene (Mlsn1). *Genomics* **54:**116–123.

2. Duncan LM, Deeds J, Cronin FE, Donovan M, Sober AJ, Kauffman M, and McCarthy JJ (2001) Melastatin expression and prognosis in cutaneous malignant melanoma. *J Clin Oncol* **19:**568–576.

3. Fang D and Setaluri V (2000) Expression and up-regulation of alternatively spliced transcripts of melastatin, a melanoma metastasis-related gene, in human melanoma cells. *Biochem Biophys Res Commun* **279:**53–61.

4. Xu XZ, Moebius F, Gill DL, and Montell C (2001) Regulation of melastatin, a TRP-related protein, through interaction with a cytoplasmic isoform. *Proc Natl Acad Sci USA* **98:**10692–10697.

TABLE 15
TRPM2 channel

Channel name	TRPM2[1–7]
Description	Nucleotide-sensing TRP channel
Other names	TRPC7, LTRPC2
Molecular information	Human unigene: Hs0.369759, chr. 21q22.3 Mouse unigene: Mm0.276762, chr. 10 C1
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging
Current	Weakly voltage-sensitive cation current
Conductance	60pS, 58pS (negative potentials); 76pS at positive potentials H_2O_2-induced channel (52.3pS), β-NAD^+-activated channel (59pS)
Ion selectivity	Nonselective, permeant to Na^+, Ca^{2+}, and K^+
Activation	Redox sensor, activation by H_2O_2 and TNF-α; modulated by arachidonic acid
Inactivation	Flufenamic acid, clotrimazole, econazole, PARP inhibitors
Activators	ADP-ribose, β-NAD^+, increased $[Ca^{2+}]_i$ potentiates (EC_{50} = 340 nM)
Gating inhibitors	None
Blockers	None
Radioligands	None
Channel distribution	Brain, placenta, lung, spinal cord, spleen, lymphocytes
Physiological functions	Not established
Mutations and pathophysiology	Not established
Pharmacological significance	Not established

chr., chromosome; NAD, nicotinamide adenine dinucleotide; TNF, tumor necrosis factor; PARP, poly(ADP-ribose) polymerase.

1. Nagamine K, Kudoh J, Minoshima S, Kawasaki K, Asakawa S, Ito F, and Shimizu N (1998) Molecular cloning of a novel putative Ca^{2+} channel protein (TRPC7) highly expressed in brain. *Genomics* **54:**124–131.

2. Perraud AL, Fleig A, Dunn CA, Bagley LA, Launay P, Schmitz C, Stokes AJ, Zhu Q, Bessman MJ, Penner R, et al. (2001) ADP-ribose gating of the calcium-permeable LTRPC2 channel revealed by Nudix motif homology. *Nature (Lond)* **411:**595–599.

3. Sano Y, Inamura K, Miyake A, Mochizuki S, Yokoi H, Matsushime H, and Furuichi K (2001) Immunocyte Ca^{2+} influx system mediated by LTRPC2. *Science (Wash DC)* **293:**1327–1330.

4. Hara Y, Wakamori M, Ishii M, Maeno E, Nishida M, Yoshida T, Yamada H, Shimizu S, Mori E, Kudoh J, et al. (2002) LTRPC2 Ca^{2+}-permeable channel activated by changes in redox status confers susceptibility to cell death. *Mol Cell* **9:**163–173.

5. Hill K, McNulty S, and Randall AD (2004) Inhibition of TRPM2 channels by the antifungal agents clotrimazole and econazole. *Naunyn Schmiedeberg's Arch Pharmacol* **370:**227–237.

6. Fonfria E, Marshall IC, Benham CD, Boyfield I, Brown JD, Hill K, Hughes JP, Skaper SD, and McNulty S (2004) TRPM2 channel opening in response to oxidative stress is dependent on activation of poly(ADP-ribose) polymerase. *Br J Pharmacol* **143:**186–192.

7. Kraft R, Grimm C, Grosse K, Hoffmann A, Sauerbruch S, Kettenmann H, Schultz G, Harteneck C (2004) Hydrogen peroxide, and ADP-ribose induce TRPM2-mediated calcium influx and cation currents in microglia. *Am J Physiol Cell Physiol* **286:**C129–C137.

TABLE 16
TRPM3 channel

Channel name	TRPM3[1–3]
Description	Melastatin-related channel
Other names	hKIAA1616, LTRPC3
Molecular information	Human unigene: Hs0.47288, chr. 9q21.11 Mouse unigene: Mm0.124567, chr. 19 B
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging
Current	near linear I–V
Conductance	83pS (140 mM symmetrical Na)
Ion selectivity	P_{Na}/P_{Ca} ~0.6 nonselective cationic
Activation	Constitutive, enhanced by hypo-osmolarity, sphingolipids
Inactivation	Independent of $[Ca^{2+}]_i$
Activators	Sphingolipids
Gating inhibitors	None
Blockers	Gd^{3+} (100 μM), insensitive to ruthenium red (1 μM)
Radioligands	None
Channel distribution	Widely expressed, kidney, brain
Physiological functions	Ca^{2+} absorption in renal collecting tubule
Mutations and pathophysiology	Not established
Pharmacological significance	Not established

chr., chromosome.

1. Grimm C, Kraft R, Sauerbruch S, Schultz G, and Harteneck C (2003) Molecular and functional characterization of the melastatin-related cation channel TRPM3. *J Biol Chem* **278:**21493–21501.

2. Lee N, Chen J, Sun L, Wu S, Gray KR, Rich A, Huang M, Lin JH, Feder JN, Janovitz EB, et al. (2003) Expression and characterization of human transient receptor potential melastatin 3 (hTRPM3) *J Biol Chem* **278:**20890–20897.

3. Grimm C, Kraft R, Schultz G, and Harteneck C (2004) Activation of the melastatin-related cation channel TRPM3 by D-*erythro*-sphingosine. *Mol Pharmacol* **67:**798–805.

TABLE 17
TRPM4 channel

Channel name	TRPM4[1–5]
Description	Ca^{2+}-activated Na^+ channel
Other names	FLJ20041, LTRPC4, TRPM4b
Molecular information	Human unigene: Hs0.467101, chr. 19q13.33 Mouse unigene: Mm0.349430, chr. 7 B3
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging
Current	Steep outward rectification >0 mV; instantaneous I–V linear
Conductance	25pS (isotonic monovalent)
Ion selectivity	P_{Na}/P_{Ca} ~100 (M4b)
Activation	K_{act}: 300–500 nM $[Ca^{2+}]_i$; >1 μM
Inactivation	Not established (Ca^{2+}-regulated)
Activators	$[Ca^{2+}]_i$
Gating inhibitors	None
Blockers	M4a: 80 μM La^{3+}, Gd^{3+} M4b: intracellular free ATP^{4-}, 1.7 μM, spermine, ADP
Radioligands	None
Channel distribution	Probably ubiquitous
Physiological functions	Regulation of calcium oscillations in activated T lymphocytes Myogenic cerebral artery constriction
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	VMCA is an unusual feature; decavanadate (2 μM) inhibits voltage dependence

chr., chromosome; VMCA, voltage-modulated calcium-activated.

1. Launay P, Fleig A, Perraud AL, Scharenberg AM, Penner R, and Kinet JP (2002) TRPM4 is a Ca^{2+}-activated nonselective cation channel mediating cell membrane depolarization. *Cell* **109:**397–407.

2. Nilius B, Prenen J, Droogmans G, Voets T, Vennekens R, Freichel M, Wissenbach U, and Flockerzi V (2003) Voltage dependence of the Ca^{2+}-activated cation channel TRPM4. *J Biol Chem* **278:**30813–30820.

3. Earley S, Waldron BJ, and Brayden JE (2004) Critical role for transient receptor potential channel TRPM4 in myogenic constriction of cerebral arteries. *Circ Res* **95:**922–929.

4. Launay P, Cheng H, Srivatsan S, Penner R, Fleig A, and Kinet JP (2004) TRPM4 regulates calcium oscillations after T cell activation. *Science (Wash DC)* **306:**1374–1377.

5. Nilius B, Prenen J, Voets T, and Droogmans G (2004) Intracellular nucleotides and polyamines inhibit the Ca^{2+}-activated cation channel TRPM4b. *Pflugers Arch Eur J Physiol* **448:**70–75.

TABLE 18
TRPM5 channel

Channel name	TRPM5[1–3]
Description	Nonselective, monovalent cation channel
Other names	Mtr1, LTRPC5
Molecular information	Human unigene: Hs0.272287, chr. 11p15.5 Mouse unigene: Mm0.286668, chr. 7 F5
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging
Current	Steep outward rectification >0 mV
Conductance	23pS (isotonic monovalent)
Ion selectivity	P_{Na}/P_{Ca} = >20 (monovalent selective)
Activation	GPCR (T1R, T2R), Ggus-PLCβ2 $[Ca^{2+}]_i$ 1–100 μM
Inactivation	Not established
Activators	$[Ca^{2+}]_i$
Gating inhibitors	None
Blockers	Not established
Radioligands	None
Channel distribution	Widely distributed, eye, liver, lung, tongue, stomach
Physiological functions	Sweet, bitter, umami taste transduction
Mutations and pathophysiology	Not established
Pharmacological significance	Not established
Comments	VMCA is an unusual feature; candidate gene for rhabdomyosarcomas, Wilms' tumor, and Beckwith-Wiedemann syndrome

chr., chromosome; GPCR, G protein-coupled receptor; VMCA, voltage-modulated calcium-activated.

1. Hofmann T, Chubanov V, Gudermann T, and Montell C (2003) TRPM5 is a voltage-modulated and Ca^{2+}-activated monovalent selective cation channel. *Curr Biol* **13:**1153–1158.

2. Liu D and Liman ER (2003) Intracellular Ca^{2+} and the phospholipid PIP2 regulate the taste transduction ion channel TRPM5. *Proc Natl Acad Sci USA* **100:**15160–15165.

3. Prawitt D, Monteilh-Zoller MK, Brixel L, Spangenberg C, Zabel B, Fleig A, and Penner R (2003) TRPM5 is a transient Ca^{2+}-activated cation channel responding to rapid changes in $[Ca^{2+}]_i$. *Proc Natl Acad Sci USA* **100:**15166–15171.

TABLE 19
TRPM6 channel

Channel name	TRPM6[1–4]
Description	Channel-kinase TRP channel
Other names	ChaK2
Molecular information	Human unigene: Hs0.272225, chr. 9q21.13 Mouse unigene: Mm0.215171, chr. 19 B
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging
Current	Steeply outward rectifying >0 mV
Conductance	Not established
Ion selectivity	Nonselective cationic, Mg^{2+} permeant
Activation	Not established
Inactivation	Not established
Activators	None
Gating inhibitors	None
Blockers	Ruthenium red
Radioligands	None
Channel distribution	Widely distributed, kidney, gastrointestinal tract
Physiological functions	Renal and gastrointestinal Mg^{2+} uptake
Mutations and pathophysiology	Human hypomagnesemia with secondary hypocalcemia (HGH)
Pharmacological significance	Not established
Comments	Contains a protein kinase on its C terminus as part of the protein (chanzyme); currently difficult to separate from TRPM7 current

chr., chromosome.

1. Ryazanova LV, Pavur KS, Petrov N, Dorovkov MV, and Ryazanov AG (2001) Novel type of signaling molecules: protein kinases covalently linked with ion channels. *Mol Biol* **35:**271–283.

2. Schlingmann KP, Weber S, Peters M, Niemann Nejsum L, Vitzthum H, Klingel K, Kratz M, Haddad E, Ristoff E, Dinour D, et al. (2002) Hypomagnesemia with secondary hypocalcemia is caused by mutations in TRPM6, a new member of the TRPM gene family. *Nat Genet* **31:**166–170.

3. Walder RY, Landau D, Meyer P, Shalev H, Tsolia M, Borochowitz Z, Boettger MB, Beck GE, Englehardt RK, Carmi R, et al. (2002) Mutation of TRPM6 causes familial hypomagnesemia with secondary hypocalcemia. *Nat Genet* **31:**171–174.

4. Voets T, Nilius B, Hoefs S, van der Kemp AW, Droogmans G, Bindels RJ, and Hoenderop JG (2004) TRPM6 forms the Mg^{2+} influx channel involved in intestinal and renal Mg^{2+} absorption. *J Biol Chem* **279:**19–25.

TABLE 20
TRPM7 channel

Channel name	TRPM7[1–7]
Description	Kinase TRP channel
Other names	TRP-PLIK, LTRPC7, ChaK(1)
Molecular information	Human unigene: Hs0.512894, chr. 15q21 Mouse unigene: Mm0.215171, chr. 2 F2
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging
Current	Weakly voltage-sensitive cation current
Conductance	105pS
Ion selectivity	P_{Na}/P_{Ca} = 3:1 in outward direction; Na^+, Ca^{2+}, Mg^{2+} inward
Activation	Not established
Inactivation	Activation of receptors coupled to PLC hydrolyzes PIP_2 to inactivate the channel
Activators	PIP_2
Gating inhibitors	None
Blockers	Mg^{2+} (EC_{50} ~ 0.6 mM), La^{3+}, polyamines
Radioligands	None
Channel distribution	Ubiquitous
Physiological functions	Cellular Mg^{2+} homeostasis proposed; potential for other trace metals, such as Zn^{2+}, Mn^{2+}; oxygen-glucose deprivation-induced calcium influx and neuronal death
Mutations and pathophysiology	Lethal in DT-40 cell line
Pharmacological significance	Not established
Comments	TRPM7 is a bifunctional protein with both ion channel and kinase activities; the protein autophosphorylates, but no other substrates are known

chr., chromosome.

1. Runnels LW, Yue L, and Clapham DE (2002) The TRPM7 channel is inactivated by PIP_2 hydrolysis. *Nat Cell Biol* **4:**329–336.
2. Runnels LW, Yue L, and Clapham DE (2001) TRP-PLIK, a bifunctional protein with kinase and ion channel activities. *Science (Wash DC)* **291:**1043–1047.
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5. Yamaguchi H, Matsushita M, Nairn AC, and Kuriyan J (2001) Crystal structure of the atypical protein kinase domain of a TRP channel with phosphotransferase activity. *Mol Cell* **7:**1047–1057.
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7. Kerschbaum HH, Kozak JA, and Cahalan MD (2003) Polyvalent cations as permeant probes of MIC and TRPM7 pores. *Biophys J* **84:**2293–2305.

TABLE 21
TRPM8 channel

Channel name	TRPM8[1–5]
Description	Cooling and menthol-sensing TRP channel
Other names	CMR1 (cold and menthol receptor), Trp-p8
Molecular information	Human unigene: Hs0.366053, chr. 2q37.1 Mouse unigene: Mm0.218753, chr. 1 D
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging
Current	Steeply outwardly rectifying >0 mV
Conductance	83pS (slope conductance)
Ion selectivity	P_{Na}/P_{Ca} = 0.3, nonselective cation channel
Activation	8–26°C
Inactivation	Warming >28°C
Activators	Cooling below 22–26°C, cooling agents such as menthol (EC_{50} = 70 μM) and icilin (EC_{50} = 360 nM); less potent: linalool, geraniol, hydroxycitronella
Gating inhibitors	None
Blockers	BCTC, thio-BCTC, capsazepine
Radioligands	None
Channel distribution	Small sensory neurons of trigeminal ganglion and dorsal root ganglia, prostate epithelium
Physiological functions	Cold sensation
Mutations and pathophysiology	Not established
Pharmacological significance	Putative menthol receptor
Comments	The neuronal colocalization and potential coassembly of TRPV1, TRPV2, TRPV3, and TRPM8 are under study

chr., chromosome.

1. McKemy DD, Neuhausser WM, and Julius D (2002) Identification of a cold receptor reveals a general role for TRP channels in thermosensation. *Nature (Lond)* **416:**52–58.
2. Peir AM, Moqrich A, Hergarden AC, Reeve AJ, Andersson DA, Story GM, Earley TJ, Dragoni I, McIntyre P, Bevan S, et al. (2002) A TRP channel that senses cold stimuli and menthol. *Cell* **108:**705–715.
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4. Brauchi S, Orio P, and Latorre R (2004) Clues to understanding cold sensation: thermodynamics and electrophysiological analysis of the cold receptor TRPM8. *Proc Natl Acad Sci USA* **101:**15494–15499.
5. Behrendt HJ, Germann T, Gillen C, Hatt H, and Jostock R (2004) Characterization of the mouse cold-menthol receptor TRPM8 and vanilloid receptor type-1 VR1 using a fluorometric imaging plate reader (FLIPR) assay. *Br J Pharmacol* **141:**737–745.

TABLE 22
TRPA1 channel

Channel name	TRPA1[1–3]
Description	Nonselective cation channel subunit
Other names	ANKTM1 (ankyrin transmembrane protein 1)
Molecular information	Human unigene: Hs0.137674, chr. 8q13 Mouse unigene: Mm0.186329, chr. 1 A3
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging
Current	Moderately outward rectifying >0 mV
Conductance	Not established
Ion selectivity	P_{Na}/P_{Ca} ~0.7
Activation	Mustard oils, PLC-coupled GPCRs, icilin, cannabinoids, cold?, mechanosensation?
Inactivation	Not established
Activators	Icilin (100 μM)
Gating inhibitors	None
Blockers	Ruthenium red (5 μM)
Radioligands	None
Channel distribution	Expressed in sensory neurons of trigeminal and dorsal root ganglia; ear
Physiological functions	Sensitive to plant-derived irritants such as mustard oils and perhaps to membrane/cytoskeletal perturbations such as stretch (as the hearing transduction channel); may depolarize nociceptors in response to pro-algesic agents (e.g. bradykinin, serotonin, and histamine) that activate PLC-coupled receptors; originally proposed to sense painfully cold temperatures
Mutations and pathophysiology	Not established
Pharmacological significance	Putative wasabi receptor
Comments	Expressed by a subset of TRPV1-expressing sensory neurons Decreased in fibroblasts after oncogenic transformation

chr., chromosome; GPCR, G protein-coupled receptor.

1. Story GM, Peier AM, Reeve AJ, Eid SR, Mosbacher J, Hricik TR, Earley TJ, Hergarden AC, Andersson DA, Hwang SW, et al. (2003) ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. *Cell* **112:**819–829.

2. Jordt SE, Bautista DM, Chuang HH, McKemy DD, Zygmunt PM, Hogestatt ED, Meng ID, and Julius D (2004) Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. *Nature (Lond)* **427:**260–265.

3. Corey DP, Garcia-Anoveros J, Holt JR, Kwan KY, Lin SY, Vollrath MA, Amalfitano A, Cheung EL, Derfler BH, Duggan A, et al. (2004) TRPA1 is a candidate for the mechanosensitive transduction channel of vertebrate hair cells. *Nature (Lond)* **432:**723–730.

TABLE 23
TRPP1 channel

Channel name	TRPP1[1–5]
Description	Nonselective cation channel subunit
Other names	PC2, PKD2, TRPP2
Molecular information	Human unigene: Hs0.181272, chr. 4q21–23 Mouse unigene: Mm0.6442, chr. 5
Associated subunits	PKD1, Hax-1, cortactin, tropomyosin, actin cadherin via PKD1
Functional assays	Patch-clamp, calcium imaging
Current	Near linear when coexpressed with PKD1
Conductance	40pS in high $[Ca^{2+}]$[4], ~50pS in symmetrical 140 mM K^{+}[5]
Ion selectivity	P_{Na}/P_{Ca} ~0.7
Activation	Mechanical stress?
Inactivation	Not established
Gating inhibitors	None
Blockers	Amiloride (30 μM), Gd^{3+}, La^{3+}
Radioligands	None
Channel distribution	Widely expressed; kidney, pancreas, heart, testis, blood
Physiological functions	Mouse cardiac, skeletal, and renal development; kidney and liver cyst formation, with PC2 (PKD2) mechanosensation in cilia (kidney)
Mutations and pathophysiology	Not established
Comments	Homomeric vs. heteromeric (with PKD1) channel function not clear; note that the nomenclature is not settled by HUGO—here we have grouped only the 6TM subtypes as TRPPs and left the longer (11TMs such as PKD1) polycystins out of the classification

chr., chromosome; PC2, polycystin-2; PKD2, polycystic kidney disease protein 2; PKD1, polycystin-1.

1. Wu G, D'Agati V, Cai Y, Markowitz G, Park JH, Reynolds DM, Maeda Y, Le TC, Hou H Jr, Kucherlapati R, et al. (1998) Somatic inactivation of Pkd2 results in polycystic kidney disease. *Cell* **93:**177–188.

2. Delmas P (2004) Polycystins: from mechanosensation to gene regulation. *Cell* **118:**145–148.

3. Tsiokas L, Arnould T, Zhu C, Kim E, Walz G, and Sukhatme VP (1999) Specific association of the gene product of PKD2 with the TRPC1 channel. *Proc Natl Acad Sci USA* **96:**3934–3939.

4. Gonzalez-Perret S, Kim K, Ibarra C, Damiano AE, Zotta E, Batelli M, Harris PC, Reisin IL, Arnaout MA, and Cantiello HF (2001) Polycystin-2, the protein mutated in autosomal dominant polycystic kidney disease (ADPKD), is a Ca^{2+}-permeable nonselective cation channel. *Proc Natl Acad Sci USA* **98:**1182–1187.

5. Luo Y, Vassilev PM, Li X, Kawanabe Y, and Zhou J (2003) Native polycystin 2 functions as a plasma membrane Ca^{2+}-permeablecation channel in renal epithelia. *Mol Cell Biol* **23:**2600–2607.

TABLE 24
TRPP2 channel

Channel name	TRPP2[1]
Description	Nonselective cation channel subunit
Other names	PKD2L1, TRPP3
Molecular information	Human unigene: Hs0.159241, chr. 10q24 Mouse unigene: Mm.308481
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging
Current	Near linear
Conductance	137pS in 100 mM Na^+
Ion selectivity	P_{Na}/P_{Ca} ~1:4
Inactivation	Not established
Activators	1 μM $[Ca^{2+}]_i$
Gating inhibitors	None
Blockers	Not established
Radioligands	None
Channel distribution	Eye, kidney, testis
Physiological functions	Involved in kidney and retinal development based on krd (P3−/−mouse)
Mutations and pathophysiology	Not established
Comments	Electrophysiological properties not firmly established; note that the nomenclature is not settled by HUGO—here we have grouped only the 6TM subtypes as TRPPs and left the longer (11TMs such as PKD1) polycystins out of the classification

chr., chromosome; PKD2L1, polycystic kidney disease protein 2-like protein 1.

1. Nomura H, Turco AE, Pei Y, Kalaydjieva L, Schiavello T, Weremowicz S, Ji W, Morton CC, Meisler M, Reeders ST, et al. (1998) Identification of PKDL, a novel polycystic kidney disease 2-like gene whose murine homologue is deleted in mice with kidney and retinal defects. *J Biol Chem* **273:**25967–25973.

TABLE 25
TRPP3 channel

Channel name	TRPP3[1]
Description	Nonselective cation channel subunit
Other names	PKD2L2, TRPP5
Molecular information	Human unigene: Hs0.546413, chr. 19p13.3-p13.2 Mouse unigene: Mm0.8356, chr. 8
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging
Current	Not established
Conductance	83pS in 100 mM Na^+
Ion selectivity	P_{Na}/P_{Ca} ~1
Activation	Not established
Inactivation	Not established
Activators	$[Ca^{2+}]_i$?
Gating inhibitors	Not established
Blockers	Not established
Radioligands	Not established
Channel distribution	Near ubiquitous
Physiological functions	Role in sorting/transport in late endocytic pathway; defective in mucolipidosis type IV lysosomal storage disease
Mutations and pathophysiology	Not established
Comments	Electrophysiological properties not firmly established; note that the nomenclature is not settled by HUGO—here we have grouped only the 6TM subtypes as TRPPs and left the longer (11TMs such as PKD1) polycystins out of the classification

chr., chromosome; PKD2L2, polycystic kidney disease protein 2-like protein 2.

1. Guo L, Schreiber TH, Weremowicz S, Morton CC, Lee C, and Zhou J (2000) Identification and characterization of a novel polycystin family member, polycystin-L2, in mouse and human: sequence, expression, alternative splicing, and chromosomal localization. *Genomics* **64:**241–251.

TABLE 26
TRPML1 channel

Channel name	TRPML1[1,2]
Description	Nonselective cation channel subunit
Other names	MCOLN1, mucolipin 1
Molecular information	Human unigene: Hs0.310431, chr. 5q31 Mouse unigene: Mm0.226899, chr. 18 C
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging
Current	Not established
Conductance	300pS?
Ion selectivity	$P_{Na}/P_{Ca} \sim 1$
Activation	Not established
Inactivation	Not established
Activators	$[Ca^{2+}]_i$?
Gating inhibitors	Not established
Blockers	Amiloride (130 μM), Gd^{3+}, La^{3+}, Ni^{2+}
Radioligands	Not established
Channel distribution	Widely expressed, heart kidney, testis, blood
Physiological functions	Not established
Mutations and pathophysiology	Not established
Comments	Electrophysiological properties not firmly established

chr., chromosome.

1. LaPlante JM, Falardeau J, Sun M, KanazirskaM, Brown EM, Slaugenhaupt SA, and Vassilev PM (2002) Identification and characterization of the single channel function of human mucolipin-1 implicated in mucolipidosis type IV, a disorder affecting the lysosomal pathway. *FEBS Lett* **532:**183–187.

2. LaPlante JM, Ye CP, Quinn SJ, Goldin E, Brown EM, Slaugenhaupt SA, and Vassilev PM (2004) Functional links between mucolipin-1 and Ca^{2+}-dependent membrane trafficking in mucolipidosis IV. *Biochem Biophys Res Commun* **322:**1384–1391.

TABLE 27
TRPML2 channel

Channel name	TRPML2[1]
Description	Nonselective cation channel subunit
Other names	MCOLN2, mucolipin 2
Molecular information	Human unigene: Hs0.459526, chr. 1p22 Mouse unigene: Mm0.116862, chr. 3
Associated subunits	Not established
Functional assays	Not established
Current	Not established
Conductance	Not established
Ion selectivity	Not established
Activation	Not established
Inactivation	Not established
Activators	Not established
Gating inhibitors	Not established
Blockers	Not established
Radioligands	Not established
Channel distribution	Widely expressed
Physiological functions	Not established
Mutations and pathophysiology	Not established

chr., chromosome.

1. Di Palma F, Belyantseva IA, Kim HJ, Vogt TF, Kachar B, and Noben-Trauth K (2002) Mutations in Mcoln3 associated with deafness and pigmentation defects in varitint-waddler (Va) mice. *Proc Natl Acad Sci USA* **99:**14994–14999.

TABLE 28
TRPML3 channel

Channel name	TRPML3[1]
Description	Nonselective cation channel subunit
Other names	MCOLN3, mucolipin 3
Molecular information	Human unigene: Hs0.535239, chr. 1p22.3 Mouse unigene: Mm0.114683, chr. 3
Associated subunits	Not established
Functional assays	Patch-clamp, calcium imaging
Current	Not established
Conductance	Not established
Ion selectivity	Not established
Activation	Not established
Inactivation	Not established
Activators	Not established
Gating inhibitors	Not established
Blockers	Not established
Radioligands	Not established
Channel distribution	Widely expressed
Physiological functions	Hair cell, stereocilia maturation
Mutations and pathophysiology	Not established
Comments	Va

chr., chromosome; Va, Varitint-waddler mouse.

1. Di Palma F, Belyantseva IA, Kim HJ, Vogt TF, Kachar B, and Noben-Trauth K (2002) Mutations in Mcoln3 associated with deafness and pigmentation defects in varitint-waddler (Va) mice. *Proc Natl Acad Sci USA* **99:**14994–14999.