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Introduction

TRP channels in disease

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Abstract

"Transient receptor potential" cation channels (TRP channels) play a unique role as cell sensors, are involved in a plethora of Ca^{2+}-mediated cell functions, and play a role as "gate-keepers" in many homeostatic processes such as Ca^{2+} and Mg^{2+} reabsorption. The variety of functions to which TRP channels contribute and the polymodal character of their activation predict that failures in correct channel gating or permeation will likely contribute to complex pathophysiological mechanisms. Dysfunctions of TRPs cause human diseases but are also involved in a complex manner to contribute and determine the progress of several diseases. Contributions to this special issue discuss channelopathias for which mutations in TRP channels that induce "loss-" or "gain-of-function" of the channel and can be considered "disease-causing" have been identified. The role of TRPs will be further elucidated in complex diseases of the intestinal, renal, urogenital, respiratory, and cardiovascular systems. Finally, the role of TRPs will be discussed in neuronal diseases and neurodegenerative disorders.

Keywords: TRP channel; Channelopathy; Hereditary disease; Systemic disease; Transgenic model

1. Introduction

The transient receptor potential (TRP) superfamily comprises now 28 mammalian cation channels which are subdivided – based on structural homology – into six subfamilies. TRP channels are expressed in almost every tissue and cell type, are activated by a plethora of different mechanisms and play an important role in various cell functions. TRP channels play an important role the pathogenesis of several human diseases [1–4]. This special issue provides in-depth reviews of the impact of TRP channels on some inherited and systemic diseases. Because of our limited knowledge of TRP channel function in native tissues, we are still at the very beginning of mechanistically understanding the role of TRPs in diseases. Only a few channelopathias in which defects in trp genes directly cause cellular dysfunction have been identified. Other indications of a crucial role of TRPs in diseases arise from our knowledge of TRP channels as targets for irritants, toxins, inflammation products, and xenobiotics and finally from the correlation between levels of channel expression and disease symptoms. Without any doubt, TRPs are important players in several human diseases and provide novel targets for pharmacological intervention. However, we are still confronted with the sparse in vivo studies, the lack of selective tools with which to modulate and even to trace TRPs, and the limited answers from studies in transgenic animals. Therefore, this special issue will also try to critically balance hopes and obstacles. How far can we go to accept TRP channels as critical players in human diseases and novel pharmacological targets?

2. TRP channels: the basics

Transient receptor potential (TRP) channels are cation channels, which act as cellular sensors in many cells types, are involved in ion homeostasis by providing route for transcellular transport, and are involved in the regulation of the function of intracellular organelles. Most of them provide Ca^{2+} entry pathways, which contribute to the regulation of a plethora of Ca^{2+}-dependent cell functions ranging from gene transcription and cell death. Likely, no cell in our body is devoid of TRPs. Topologically, each TRP channel subunit consists of six putative transmembrane spanning segments (S1–6), a pore-

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forming loop between S5 and S6, and intracellular located –NH_2 and –COOH termini. Assembly of channel subunits as homo- or hetero-tetramers results in the formation of cation selective channels. Based on amino acid homology, the TRP superfamily can be divided into seven subfamilies (see Fig. 1) (see for detailed reviews [2,3,5,6, 7,8,9,10,11,12,13], series of books and special issues [14], "TRP channels: Facts, Fiction, Challenges," Cell Calcium 33, 2003; "Functional Role of TRP Channels" Pflügers Archive Eur J Physiol, 451, 2005), and also data bases such as Ensemble Genome Browser at http://www.ensembl.org/). The TRPC (canonical) subfamily consists of seven (TRPC1–7) and the TRPM (melastatin) subfamily of eight different channels (TRPM1–8). The TRPV (vanilloid) subfamily presently comprises six members (TRPV1–6) and the most recently discovered subfamily, TRPA (ankyrin), has only one mammalian member (TRPA1). The TRPP (polycystin) and TRPML (mucolipin) families, each containing 3 mammalian members, are relatively poorly characterized, but are attracting increasing interest because of their involvement in several human diseases.

Most of the functionally characterized TRP channels are non-selective Ca^{2+}-permeable cation channels. Only TRPM4 and TRPM5 are only permeable to monovalent cations but not to Ca^{2+} or Mg^{2+}. Two mammalian TRPs, TRPV5 and TRPV6, are highly Ca^{2+} permeable. TRPM6 and TRPM7 are highly permeable to Mg^{2+}. At least three TRP channels, TRPV1, TRPML1, and TRPP3, are also highly permeable to H^+ ions.

As far as gating of TRP channels is concerned, no unifying mechanism exists. Characteristically, most of the TRP channels can be activated by various chemical or physical stimuli, such as ligand binding, temperature, changes in osmolarity or cell volume, mechanical forces, or voltage. Some TRP channels (such as TRPV5, TRPV6, and probably TRPA1) are constitutively open, although most of these data originate from experiments in heterologous overexpression systems. TRPC channels are gated via PLC activation, either directly by diacylglycerol (DAG), such as TRPC2, TRPC3, TRPC6, and TRPC7, or indirectly via still not yet identified mechanism (TRPC1, TRPC4, TRPC5). Indeed, TRPC1, TRPC4, and TRPC5, which are activated by receptor-induced PLC, are completely unresponsive to DAG [37,38]. The mechanisms by which PLC activates these channels remain controversial.

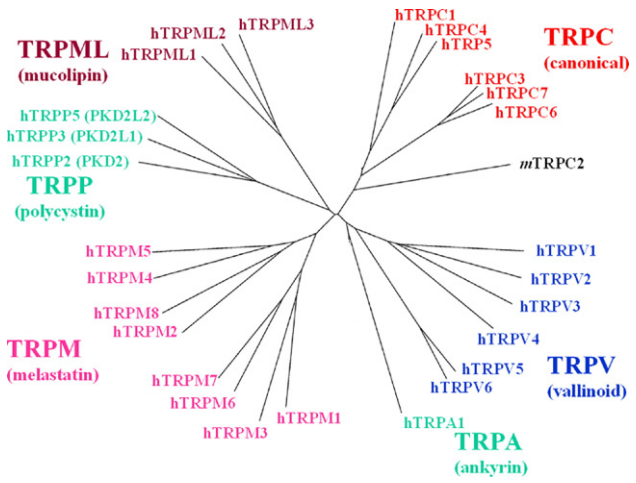

Fig. 1. Phylogenetic tree of the mammalian (human) TRP channel superfamily. TRPC (canonical), TRPM (melastatin), TRPV (vanilloid), TRPA (ankyrin), TRPP (polycystin), and TRPML (mucolipin). *trpc2* is a pseudogene in humans.

Several TRP channels are activated by changes in temperature, e.g., by heat (TRPV1, TRPV2, TRPV3, TRPV4, TRPM2, TRPM4, TRPM5) or by cold (TRPM8, and probably indirectly TRPA1). Other TRP channels have recently been identified, although not yet generally accepted, as mechano-sensor channels (TRPC1, TRPC6, TRPP2, TRPV4, TRPV2?; TRPM4?, TRPM7?) or as channels activated by hyposmotic cell swelling (TRPV2, TRPV4, TRPM3) or cell shrinking (TRPA1). The role of TRPA1 as a mechano-sensor channel is still under debate. At least two TRP channels can be gated by a decreased in pH: TRPV1 and TRPP3. For most of the TRP channels, activating ligands have been discovered and are endogenous (e.g., for TRV1 endocannabinoids such as anandamide; see Tables 1 and 2), derived from natural compounds such as black pepper, camphor, oregon, or carvacrol with as best-studied examples capsaicin for TRPV1 and menthol for TRPM8, or purely synthetic compounds (e.g., the phorbol 4α-phorbol 12,13-didecanoate for TRPV4).

Tables 1 and 2 summarize some essential properties of TRP channel, which might be helpful for the following articles.

3. The TRP channel family and diseases

Defects in ion channel function have an increasing impact on our understanding of several diseases. Diseases caused by channel dysfunction are known as channelopathias. Of the approximately 300 ion channels predicted in the human genome (http://www.ncbi.nlm.nih.gov/RefSeq; http://www.celeradiscoverysystem.com), relatively few have been directly connected to human diseases [55,56]. For a series of more general reviews on the role of TRP channels in disease see [1–4].

In this special issue, TRP channelopathias which link defects in the gene encoding the channels with a disease or disease symptoms are described. Six TRP channel-related channelopathies in which mutants in the gene cause "loss-of-function" or "gain-of-function" ion channels have been identified to date (see Table 3 and the detailed reviews in this special issue for focal segmental glomerulosclerosis TRPC6, mucolipidosis type IV TRPML1, hypomagnesemia with secondary hypocalcemia TRPM6, polycystic kidney disease TRPP1/TRPP2, aromatase excess syndrome TRPM7, and eventually Guamanian amyotrophic lateral sclerosis (ALS-G) and Guamian Parkinsonism dementia (PD-G) TRPM7). Other diseases can be provoked by changes in channel abundance, or channel sensitization, or desensitization, resulting in potentiated or abolished responses to pathological stimuli. Production of endogenous ligands for TRP channels during the development of a disease, e.g., during inflammation, can affect channel function and cause diseases. The involvement of TRPV1 in pain reception and the generation of neuropathic pain give an excellent example of how mechanisms of modulation of channel activity can cause and affect the development of many

Table 1
Some properties of the TRPC and TRPV family members

	Permeation	Proposed activation mechanisms
TRPC1 ENSG00000144935	nonselective, Ca^{2+} permeable	phospholipase C (PLC), 1-oleoyl-2-acetyl-*sn*-glycerol (OAG), mechanical (stretch), phosphoinositide-3 kinase (PI3K), calmodulin, tyrosine-kinase receptor (TKR)-PLCγ, upregulated by hypoxia-inducible factor (HIF-1), PKC, NO?, store depletion?
TRPC2 ENSMUSG00000058020	nonselective, Ca^{2+} permeable	PLC, diacylglycerol (DAG), store depletion?
TRPC3 ENSG00000138741	nonselective, Ca^{2+} permeable	PLC, DAG, OAG, brain-derived growth factor (BDNF)—TKR-PLCγ, tyrosine protein kinase Src, inositol (1,4,5) trisphosphate receptor (IP_3-R), orexin receptor OX_1R, store depletion?; *inhibited by NO and protein kinase G (PKG)*,
TRPC4 ENSG00000100991	nonselective, Ca^{2+} permeable	PLC, GTPγS, micromolar La^{3+}, NO? Store depletion?
TRPC5 ENSG00000072315	nonselective, Ca^{2+} permeable	PLC, GTPγS, receptor-operated, lysophosphatidylcholine (LPC), micromolar La^{3+} or Gd^{3+}, store depletion? $[Ca^{2+}]_e$, modest elevation of $[Ca^{2+}]_i$, phosphatidylinositol 4-phosphate 5-kinase (PIP5K), Rho GTPases (e.g. Rac1), PI3K), yosin light chain kinase (MLCK), NO nitrosylation of pore cysteines
TRPC6 ENSG00000137672	nonselective, Ca^{2+} permeable	PLC, DAG, OAG, Src, 20-hydroxyeicosatetraenoic acid (20-HETE,) tyrosine kinase Fyn, Ca^{2+}—Camodulin kinase II (CamK-II), mechano-activated, AlF_4^-, flufenamate; *inhibited by the tarantula peptide toxin GsMTx-4*,
TRPC7 ENSG00000069018	nonselective, Ca^{2+} permeable	PLC?, DAG, OAG, 20-HETE, store depletion?
TRPV1 ENSG00000043316	nonselective, Ca^{2+} permeable	Depolarization, heat (≥43 °C), low pH (≤5.9), vanilloids, endovanilloids, protein kinase C (PKC), CamK-II, PI(3)kinase, activated by cyclin-dependent kinase (Cdk)-5, anandamide, nerve growth factor (NGF), glia-derived growth factor (GDGF), neurotropin 3 (NT3), reducing agents like dithiothreitol (DTT), sensitization by ethanol, jelly fish toxin, venoms of the Indian tarantulas contain inhibitor cysteine knot peptides (ICK), 12/15-hydroperoxyeicosatetraenoic acid (12-(S)-HPETE, 15-(S)-HPETE), 5-(S)-HETE, leukotriene B_4, N-arachidonoyl dopamine (NADA), protease-activated receptor 2 (PAR2), spermine, 2-aminoethoxydiphenyl borate (2-APB), oleoylethanolamide (OEA), protein kinase A (PKA), PGE_2 and PGI_2 via their receptor EP_1 or IP; metabotropic 5-hydroxytryptamine (5HT) receptors, $5HT_{2A}R$ and $5HT_7R$, *decreased PI(4,5)P_2 (?)*(PIP_2 also activates directly), *inhibited by stretch (short splice variant)*
TRPV2 ENSG00000154039	nonselective Ca^{2+} permeable	Noxious heat (>53 °C), mechanical (stretch, swelling),PKC, PI(3)K, growth factors, insulin growth factor 1 (IGF-1), head activator (HA), 2-APB
TRPV3 ENSG00000167723	nonselective Ca^{2+} permeable	Heat (23–29 °C), PKC, camphor, carvacrol, 2-APB, voltage dependent
TRPV4 ENSG00000111199	nonselective Ca^{2+} permeable	Moderate heat (>24°C), cell swelling, shear stress, PLA_2 activation, PKC, PAR_2, anandamide, epoxyeicosatrienoic acid (EETs), 4α-phorbol 12,13-didecanoate (4α-PDD) and other phorbols, bisandrographolide A (BAA, from a Chinese herb)
TRPV5 ENSG00000127412	highly Ca^{2+} selective	Low $[Ca^{2+}]_i$, hyperpolarization, voltage dependent block by Mg^{2+}, calbindin D_{28} prevents channel inactivation, serum- and glucocorticoid dependent kinase 1 (SGK1), serine/threonine kinase WNK4
TRPV6 ENSG00000165125	highly Ca^{2+} selective	Low $[Ca^{2+}]_i$, hyperpolarization, voltage dependent block by Mg^{2+}, Src

For relevant data bases see also the Ensemble Genome Browser at http://www.ensembl.org/. The respective TRP numbers are included. Some inhibitory effects in are mentioned in italics. For further details and references please refer to the reviews [15–24]. For more information on all TRP channels see [11,13,14,25–28], the excellent guides to TRP channels on the David Clapham laboratory website at http://www.clapham.tch.harvard.edu/, the very comprehensive and instructive tables in [29], and the special issue: "TRP channels: Facts, Fiction, Challenges", Cell Calcium 33, 2003, "Functional Role of TRP Channels" Pflügers Archive Europ J Physiol, 451, 2005, "TRP channels as novel pharmacological targets", Naunyn Schmiedebergs Arch Pharmacol, 371, 2005. For members of the TRPV family, see for details the reviews of [30–36].

diseases. TRP channels are exceptional polymodal gated channels and will therefore be able to sense many disturbances in several forms of cellular homeostasis.

In general, dysregulation of TRP channel function may lead to diseases by one or more of the following mechanisms:

- Most TRP channels play a role in Ca^{2+} signaling. Given the universal role of Ca^{2+} as a signaling molecule, dysfunctions in Ca^{2+} signaling due to altered TRP channel function can have strong effects on a variety of cellular and systemic processes. One reasonably understood example is the gain-of-function of TRPC6 in the pathogenesis of cardiac hypertrophy, in which an increased Ca^{2+} influx couples via calciceurin to NFAT activation [57].
- TRP channels can act as general polymodal cellular sensors, measuring changes in the environment to initiate adequate

Table 2
Some important properties of the TRPM, TRPML, TRPP, and TRPA family members

	Permeation	Proposed activation mechanisms
TRPM1 ENSG00000134160	n.d.	Translocation, microphthalmia-associated transcription factor (MITF) induced expression
TRPM2 ENSG00000142185	nonselective, Ca^{2+} permeable	ADP-ribose, cyclic ADP-ribose at higher temperatures, nicotinamide adenine dinucleotide (NAD), heat, H_2O_2 and other reactive oxygen species (ROS), poly(ADP)ribose polymerase-1 (PARP-1), Ca^{2+}, NAD dependent deacetylases, sirtuins
TRPM3 ENSG00000083067	nonselective, Ca^{2+} permeable	Cell swelling, store depletion?, D-erythrosphingosine, steroid hormones (pregnenolone derivatives)
TRPM4 ENSG00000130529	Selective for monovalent cations, Ca^{2+} impermeable	Elevated $[Ca^{2+}]_i$, ATP, PKC, decavanadate, voltage dependent, heat, $PI(4,5)P_2$, 3,5-bis(trifluoromethyl)pyrazole (BTP2),
TRPM5 ENSG00000070985	Selective for monovalent cations, Ca^{2+} impermeable	Elevated $[Ca^{2+}]_i$, phosphatidylinositol (4,5) bisphosphate ($PI(4,5)P_2$) Voltage dependent, heat, arachidonic acid
TRPM6 ENSG00000119121	highly Mg^{2+} permeable, Ca^{2+} permeable	Decreased $[Mg^{2+}]_i$, 2-APB
TRPM7 ENSG00000092439	highly Mg^{2+} permeable, Ca^{2+} permeable	Decreased $[Mg^{2+}]_i$, Mg-ATP, $PI(4,5)P_2$, cAMP, G-proteins, PKA, Src, shear stress, stretch, membrane translocation
TRPM8 ENSG000000144481	nonselective, Ca^{2+} permeable	Depolarization, cold (8–28 °C), menthol, icilin, increased intracellular pH, $PI(4,5)P_2$, lysophosphatides (LP's)
TRPML1 ENSG00000090674	H^+ permeable	Increased $[Ca^{2+}]_i$, *inhibited by proteolytic cleavage*
TRPML2 ENSG00000153898	n.d.	n.d.
TRPML3 ENSG00000055732	n.d.	low pH
TRPP2 ENSG00000118762	nonselective, Ca^{2+} permeable	mechanical stress, $[Ca^{2+}]_i$
TRPP3 ENSG00000107593	nonselective, Ca^{2+} permeable	$[Ca^{2+}]_i$, activated by low pH when expressed with PKD1L3.
TRPP5 ENSG00000078795	nonselective, Ca^{2+} permeable	$[Ca^{2+}]_i$
TRPA1 ENSG00000104321	nonselective, Ca^{2+} permeable	Isothiocyanates, allicin, Δ^9-tetrahydrocannabinol (THC), cinnamaldehyde, prolonged noxious cold?, mechanical stress, voltage dependent ?, $[Ca^{2+}]_i$ dependent, OAG and arachidonic acid downstream of receptor-mediated PLC activation, menthol?, thymol, carvacrol, acrolein, artemin (a neuronal survival factor), covalent modification of N-terminal cysteines activates

For references for channel names, numbering, and additional information, see the note to Table 1 (some inhibitory effects in italics). For details and references, please refer to the relevant reviews [28,39–45]. Note that TRPM4 data listed are for TRPM4b. Some important properties of members of the TRPP and TRPML families, as well as of TRPA1, are listed. Relevant reviews for TRMLs are [46–48]; for TRPPs see [9,48–53]; for TRPA see [54].

cell organ and behavioral response. Mistuning in these sensory inputs may cause multiple forms of cellular and somatosensory dysregulation.

- Some TRP channels function as gatekeepers for the selective (re)absorption of ions such as Mg^{2+} and Ca^{2+}. Dysfunction will lead to general disturbances in Mg^{2+} and Ca^{2+} homeostasis.
- TRP channels are present on intracellular membranes, where their malfunctioning may lead to disturbed organelle function. One clear example is the deregulation of lysosome function due to mutations in TRPML1 [47].
- Some TRP channels play an important role in the trafficking of interacting proteins. Mistargeting of these binding partners may underlie a variety of pathological conditions.
- Several TRP channels are involved in the control of cell proliferation and growth. Dysfunctions may lead to growth disturbances, altered organogenesis, or cancer.
- TRP channels have the potential to modulate the electrical activity of excitable cells, e.g., in brain and heart. Investigating the consequences of TRP channel dysfunction on electrically complex cell functions such as generation of spontaneous electrical activity is an important challenge for future research.

Our restricted knowledge about the function of many TRP channels and the paucity of selective modulators hamper our understanding of the mechanistic role of TRP channels in human disease and also the development of TRP targeting drugs. So far, the best understood TRP channel is TRPV1, and a plethora of blocking compounds are available for the treatment of different forms of pain (see this special issue and also, e.g., Ref. [58]). Another promising example concerns TRPC1. This channel is up-regulated in smooth muscle cells in occlusive vascular disease. Inhibitory antibodies of TRPC1 have the potential of acting as protective agents against human vascular failure [59]. Some other trials using functional antibodies are anticipated [60].

A role for several TRP channels in the ontogeny of diseases can be suspected based on the chromosomal localization of the encoding genes. The chromosomal localizations of all TRP genes and some relevant diseases linked to these loci are summarized in detail in an excellent review [1]. However, also we know these "thy neighbors," causal pathogenic mechanisms, have not yet been established (see also OMIM data base at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi%3Fdb%3DOMIM).

Finally, this introduction presents a table listing TRPs that cause diseases or contribute to their progression. Table

Table 3
Proposed functions of TRPs, chromosomal localization, and possible relationships to diseases (adapted from [3] used with permission)

	Proposed function	Channelopathy	Involvement based on functional or genetic evidence (phenotype transgenic mouse models)
TRPC1 3q22–3q24	Coupling to metabotrobic glutamate receptors, mediate slow excitatory postsynaptic currents (EPSCs), mechanosensor, growth cone guidance	n.d.	Asthma, bronchial hyperresponsiveness, chronic obstructive pulmonary disease (COPD), defective immunresponse in B cells, T cells (NFAT), heart hypertrophy, Duchenne muscular dystrophy, neurodegenrative disorders, Myotonic dystrophy type 2, hypertention, Seckel syndrome,
TRPC2 pseudogene	Pheromone sensing in mice, acrosome reaction.	n.d.	Gender recognition defect, behavioural defects
TRPC3 4q27	Brain-derived neuritrophic factor (BDNF) mediated neuronal differentiation, vasomotor function, resistence vessel, airway regulator, antigene stimulation of lymphocytes, growth cone guidance	n.d.	Pulmonary disease, idiopathic pulmonary arterial hypertension (IPAH), heart hypertrophy, essential hypertension
TRPC4 13q13.1–q13.2	Vasomotor function, microvascular permeability, GABAnergic input lateral geniculate nucleus	n.d.	Breast cancer, atopic dermatitis, asthma, COPD; Impairment endothelium-dependent vasorelaxation and endothelial barrier function,
TRPC5 Xq23	Growth cone morphology, growth cone guidance, brain development	n.d.	COPD, Coronary heart disease, X-linked mental retardation, migraine, Alzheimer's Disease
TRPC6 11q21–q22	Vasomotor function, smooth muscle, platelet aggregation, mechanosensor, important for hypoxic pulmonary vasocontriction (HPV): shift blood flow to normoxic aleveolae	proteinuric kidney disease: focal and segmental glomerulo-sclerosis (FSGS,OMIM 603965)	COPD, lung cancer, IPAH, heart hypertrophy, mucus hypersecretion in COPD, Duchenne muscular dystrophy, neurodegenerative disorders; Defective vasomotor control, sensitized myogenic response (TRPC3 upregulation), lack of HPV in *trpc6−/−*
TRPC7 5q31.1	Role in immune response	n.d.	n.d.
TRPV1 17p13.3	Sensing spicy (hot) peppers, pain sensation, noxious temperature sensing, sensor bladder distension	n.d.	Thermal hyperalgesia, allodynia, functional bowel disease (FBD), inflammatory bowel disease (Crohn, OMIM 266600), vulvodynia, osteoarthritis, pancreatitis, gastro-oesophagal reflux disease (GORD), bladder disease, cystitis, asthma, migraine, schizophrenia, pain in general (tooth pain), breast cancer, myasthenic syndrome, non-insulin-dependent diabetes mellitus, probably involved in type 1 diabetes; Alzheimer's Disease
TRPV2 17p11.2	Sensing thermal pain, mechanosensing	n.d.	Muscular dystrophia (disruption dystrophin-glycoprotein complex), cardiomyopathy, cardiac hypertophy, central areolar choroidal dystrophy, myasthenic syndrome, prostate cancer
TRPV3 17p13.3	Warm sensing, osmosensing	n.d.	Breast cancer, myasthenic syndrome, non-insulin-dependent diabetes mellitus; Defective environmental themosensation
TRPV4 12q23–24.1	Osmosensing (CNS), warm sensing, nociception, pressure sensing (DRG)	n.d.	Hypotonic hyperalgesia, mechanical hyperalgesia, allodynia, thermal hyperalgesia, central hypoventilation syndrome, cardiopathy asthma, bronchial hyperresponsiveness, neuropathic pain, autosomal nonsyndromic hearing loss (ADNSHL), impairment osmoregulation, hypertension; Defective environmental themosensation
TRPV5 7q35	Ca^{2+} reabsorption kidney (absorption in duodenum), vitamine D sensitive	n.d.	Renal tubular acidosis, cancer, defective Ca^{2+} reabsorption; Hypercalciuria, osteoporosis?, Zucker diabetic fatty rats
TRPV6 7q33–34	Ca^{2+} absorption duodenum (reabsorption in kidney)	n.d.	Renal tubular acidosis, cancer increased in prostate cancer; Ca^{2+} malabsorption, decreased fertility, alopecia, Ca^{2+} wasting, reduced bone density
TRPM1 15q13-q14	Tumour suppressor	n.d.	Down-regulation in malignant melanomas

(continued on next page)

Table 3 (*continued*)

	Proposed function	Channelopathy	Involvement based on functional or genetic evidence (phenotype transgenic mouse models)
TRPM2 21q22.3	Oxidant stress sensor in immune cells, glia respiratory bursts in neutrophils, temperature dependent, Ca^{2+} entry in pancreatic β cells	n.d.	BP-I, II (bipolar disorder), nonsyndromic hereditary Alzheimer's Disease; deafness neuronal cell death; holoprosencephaly HPE1 (OMIM 236100), Knobloch syndrome (OMIM 267750),
TRPM3 9q21.11	Ca^{2+} absorption in kidney Osmosensor, mechanosensor	n.d.	possible candidate gene for defective Ca^{2+} reabsorption, amyotrophic lateral sclerosis with frontotemporal dementia (OMIM 105550), early-onset pulverulent cataract (OMIM 605749), hemophagocytic lymphohistiocytosis (HLH, OMIM 603552), infantile nephronophthisis (OMIM 602088)
TRPM4 19q13.32	Ca^{2+} oscillation in T-lymphocytes, mast cells, pneumocytes type II, macula densa cells, negative feedback regulator for Ca^{2+} entry, Bayliss effect, slow waves in sleep, memory function in entorhinal cortex, mechanosensor, temperature dependent	n.d.	Hyperresponsiveness in immune cells, induction of proinflammatory conditions, allergy, defective surfactant secretion in pneumocytes type II, defective Bayliss effect, trigger for paroxysmal depolarization shift (PDS), spreading depression hypoxic depolarisation, stroke; Diabetes mellitus?
TRPM5 11p15.5	Sweet, bitter, umami taste, temeprature dependent	n.d.	Beckwith-Wiedemann syndrome (BWS, OMIM 602131, 602631) Diabetes mellitus, breast bladder and lung cancers
TRPM6 9q21.13	Mg^{2+} (re)absorption duodenum, kidney	Autosomal-recessive, hypomagnesaemia with secondary hypocalcaemia (HSH/HOMG 1; OMIM 602014)	Defective Mg^{2+} reabsorption, Spastic paraplegia, deafness, amyotrophic lateral sclerosis with frontotemporal dementia; Taste dysfunction
TRPM7 15q21	Mg^{2+} homeostasis, cell cycleregulation, entry pathway for tracemetals	aromatase excess syndrome (OMIM+107910), amyotrophic lateral sclerosis-parkinsonism/ dementia complex (ALS-G/PD-GGuam disease; OMIM 105500),	Target for exitotoxicity in brain, neuronal cell death, defective vascular remodelling, hypertension, stroke; Defective ossification (zebrafish model)
TRPM8 2q37.1	Cold sensing, pain pathway, sensor	n.d.	Cold hyperalgesia, up regulated in tumours of prostate, breast, colon, lung, skin, painful bladder syndrome
TRPP2 4q21–23	Cardiac and skeletal muscle and kidney development, tubulogenesis, mechanosensation in primary cilia, sperm movement	Autosomoal dominant polycystic kidney disease (ADPKD; OMIM 173910),	Cardiac septal defects, distrurbances left-right axis, organ localization, possibly associated with Bardet-Biedl syndrome, some connection with autosomal recessive polycystic kidney disease (ARPKD)

Table 3 (*continued*)

	Proposed function	Channelopathy	Involvement based on functional or genetic evidence (phenotype transgenic mouse models)
TRPP3 10q24–q25	Kidney development, retinal development	n.d.	Renal hypoplasia, optic nerve coloboma with renal disease, epilepsy, Alzheimer disease ARPKD; Kidney-retina defects (krd mouse)
TRPP5 5q31	n.d.	n.d.	ARPKD
TRPA1 8q13	Activation by pungent painfull stimuli (mustard oil, wasabi, horse radish, garlic, onions, ...), activated by bradykinin (PLC dependent), mechanotransduction channel, noxious cold	n.d.	Inflammatory pain, cold hyperalgesiam; cold hyperalgesia, mechanical pain, mechanical hypersensitivity, inflammatory pain
TRPML1 19p13.3–13.2	Intracellular protein sorting/transport, role in late endosomal pathway, endocytosis	Mucolipidosis IV (ML IV, OMIM 252650),	
TRPML2 1p22	n.d.	n.d.	Candidate gene for neurosensory disorders; associated with varitint-waddler (deaf, head-bobbing and circling, defects in vestibular balance, tricolored)
TRPML3 1p22.3	Maturation of hair cells, retina, intracellular trafficking	n.d.	Candidate gene for neurosensory disorders; associated with varitint-waddler

For details and references see text. Functional evidence of possible disease connections obtained from transgenic mouse models is marked in red. n.d., not determined. For more possible associations between TRP channels and disease based on genomic localisation see http://www.ncbi.nlm.nih.gov/entrez/query.fcgidb%3DOMIM, [14], and especially [1].

3 is intended to guide the reader through the following expert articles which will provide detailed insight into some of the here-listed connections between TRPs and diseases.

4. Conclusion

In this the roles of some TRP channels in human diseases are described by leading scientists in this field. The involvement of TRPs in a plethora of fundamental cell functions urges the investigation of their role in human pathophysiology and disease. Undoubtedly, these studies, linking TRP function to disease, will become an important priority in biomedical sciences. This special issue is also intended to describe these channels as novel and important targets for the development of new drugs. Needless to say, we have just entered an exciting and fast advancing field of ion channel research.

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