Topical Review

TRPpathies

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Many human diseases are caused by mutations in ion channels. Dissecting the pathogenesis of these 'channelopathies' has yielded important insights into the regulation of vital biological processes by ions and has become a productive tool of modern ion channel biology. One of the best examples of a synergism between the clinical and basic science aspects of a modern biological topic is cystic fibrosis. Not only did the identification of the ion channel mutated in cystic fibrosis pinpoint the root cause of this disease, but it also has significantly advanced our understanding of basic biological processes as diverse as protein folding and epithelial fluid and electrolyte secretion. The list of confirmed 'channelopathies' is growing and several members of the TRP family of ion channels have been implicated in human diseases such as mucolipidosis type IV (MLIV), autosomal dominant polycystic kidney disease (ADPKD), familial focal segmental glomerulosclerosis (FSG), hypomagnesemia with secondary hypocalcaemia (HSH), and several forms of cancer. Analysing pathogenesis of the diseases linked to TRP dysregulation provides an exciting means of identifying novel functions of TRP channels.

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Pathogenesis of some 'TRPpathies', such as HSH, appears straightforward. HSH manifests as low blood Mg^{2+} due to deficient renal and intestinal Mg^{2+} re-absorption (reviewed in Konrad *et al.* 2004). HSH has been linked to several mutations in the gene *TRPM6*, which codes for the TRPM6 channel (Schlingmann *et al.* 2002; Walder *et al.* 2002) (chromosomal localization of this and other TRP coding discussed in this review can be found in Table 1). This Mg^{2+}-selective channel is predominantly expressed in the intestinal epithelium and in the kidney (Schlingmann *et al.* 2002; Walder *et al.* 2002), and some of the mutations shown to induce HSH result in an inactive channel in recombinant system (Voets *et al.* 2004). Some other HSH-linked mutations affect TRPM6 interaction with TRPM7 (Chubanov *et al.* 2004), its close relative linked to Guamanian amyotrophic lateral sclerosis and parkinsonism dementia (Hermosura *et al.* 2005). Since many TRP channels hetero-multimerize in order to form functional channels (Strubing *et al.* 2001; Goel *et al.* 2002; Strubing *et al.* 2003), the loss of TRPM6–TRPM7 interaction results in the loss of channel function (Chubanov *et al.* 2004).

Perhaps the best-known example of a pathologically relevant TRP channel is TRPV1. Cloned as a result of a search for molecular determinants of perception of heat and the noxious compound in hot pepper, capsaicin (Caterina *et al.* 1997; Tominaga *et al.* 1998), TRPV1 seems to be involved in an array of functions involving perception of heat and chemical pain (Table 1, see also (Clapham, 2003; Nilius *et al.* 2005)). TRPV1 is clearly a promising target for pharmacological interventions into pain, cough, inflammation and urinary problems (reviewed in Nagy *et al.* 2004; Szallasi & Appendino, 2004; Jia *et al.* 2005).

The causal relationships between dysregulation of TRP channels and the corresponding genetic diseases remain obscure for several human TRPpathies. Some diseases, such as ADPKD, attracted enormous interest in recent years, which resulted in a significant degree of understanding of the physiology of the corresponding TRP channels if not of the exact connection between the channel dysregulation and the disease. As discussed below, the same is largely true for TRPC6, TRPV6 and cancer as well as for TRPC6 and FSG. Very limited information exists about localization, permeation properties or regulation of TRPM1, despite clearly documented links to skin cancer. Several recent reports, focused on the function of the lysosomal ion channel TRP-ML1, mutations in which are responsible for lysosomal storage disorder MLIV, have suggested several possible roles of this ion channel in regulating lysosomal function. The present review will focus on these TRPpathies, and will specifically discuss some unanswered questions pertaining to pathogenesis

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Table 1. TRP channels implicated in genetic disorders

TRP channel	Gene	Chromosomal localization (human/mouse)	Associated disorder	Effect of mutation	Causative relationship	References
TRP channels linked to human diseases						
TRP-ML1	*MCOLN1*	19p13.3-p13.2 8 A1.1	MLIV	Down/change in selectivity or localization	Yes	(Bassi *et al.* 2000; Sun *et al.* 2000; Bach, 2001; Slaugenhaupt, 2002; LaPlante *et al.* 2004; Manzoni; *et al.* 2004 Raychowdhury *et al.* 2004; Cantiello *et al.* 2005; Kiselyov *et al.* 2005)
TRPP2	*PKD2*	4q21-q23 5 E5	ADPK2	Down	Yes	(Koptides & Deltas, 2000; Boucher & Sandford, 2004)
TRPC6	*TRPC6*	11q21-q22 9 A1	Prostate cancer	Up	?	(Buess *et al.* 1999; Thebault *et al.* 2006)
—	—	—	FSG	Up/?	Yes/?	(Reiser *et al.* 2005; Winn *et al.* 2005)
TRPV6	*TRPV6*	7q33-q34	Prostate cancer	Up	Increased proliferation	(Peng *et al.* 2001; Wissenbach *et al.* 2001; Fixemer *et al.* 2003; Wissenbach *et al.* 2004; Schwarz *et al.* 2006)
TRPM1	*TRPM1*	15q13-q14 7 C	Cutaneous melanoma	Down	?	(Duncan *et al.* 1998; Fang & Setaluri, 2000)
TRPM6	*TRPM6*	9q21.13 19 B	Hypomagnesemiawith secondary hypocalcaemia	Down or disrupted interaction with TRPM7	Yes	(Schlingmann *et al.* 2002; Walder *et al.* 2002; Chubanov *et al.* 2004; Voets *et al.* 2004; Schlingmann *et al.* 2005)
TRPM7	*TRPM7*	15q21 2 F2	Guamanian amyotrophic lateral sclerosis, parkinsonism dementia	Mutations that increase inhibition by Mg	Yes	(Hermosura *et al.* 2005)
TRPM8	*TRPM8*	2q37.1 1 D	Prostate, breast, colon, lung, and skin tumers	Up/Down	Increased cell survival	(Tsavaler *et al.* 2001; (Fuessel *et al.* 2003; Henshall *et al.* 2003; Zhang & Barritt, 2004, 2006)
Phenotypes in mice with altered TRP channels						
TRPC2	*TRPC2*	11p15.4-p15.3 (pseudogene) 7 F1	Altered sexual and social behaviour	Knock-out	Pheromone recognition	(Leypold, 2002; Stowers *et al.* 2002)
TRPC3	*TRPC3*	4q27 3 B	Cardiac hypertrophy or cardiomyopathy	Transgenic expression of human TRPC3 in mouse heart	Ca^{2+} entry	(Nakayama *et al.* 2006)
TRPC4	*TRPC4*	13q13.1-q13.2 3 D	Impaired regulation of vascular tone and vascular permeability	Knock-out	Ca^{2+} entry	(Freichel *et al.* 2001; Tiruppathi *et al.* 2002; Freichel *et al.* 2004)
TRPC6	*TRPC6*	11q21-q22 9 A1	Blood pressure regulation	Knock-out	Regulation of smooth muscle contractility in mice	(Dietrich *et al.* 2005*b*)
TRPM5	*TRPM5*	11p15.5 7 F5	Suppressed taste; impaired thermal sensitivity of taste	Knock-out	Taste sensation, Thermosensation	(Zhang *et al.* 2003; Talavera *et al.* 2005; Damak *et al.* 2006)
—	—	—	Beckwith-Wiedemann syndrome (BWS)	?	Aberrant imprinting in the gene cluster containing TRPM5*	(Enklaar *et al.* 2000; Prawitt *et al.* 2000)
TRP-ML3	*MCOLN3*	1p22.3 3 H2	Pigmentation defects, hearing loss due to hair cell degeneration	Mutations (knock-out is perinatal lethal)	?	(Di Palma *et al.* 2002)
TRPP2	*PKD2*	4q21-q23 5 E5	Kidney cysts, liver lesions, cerebral arterial lesions	Knock-out	Mechanically induced Ca^{2+} influx	(Wu *et al.* 1998; Qian *et al.* 2003; Thomson *et al.* 2003; Gallagher *et al.* 2006)

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Table 2. Continued

TRPP3	*PKD2L1*	10q24 19 C3	Kidney and retinal defects	Deletion in the region containing *PKD2L1***	?	(Nomura *et al.* 1998)
TRPV1	*TRPV1*	17p13.3 11 B3	Abnormal bladder. contractions. Diminished heat sensation, thermal hyperalgesia, fever production,allodynia, neuropathic pain	Knock-out, Down	Mechanosensation?, Thermosensation	(Caterina *et al.* 2000; Davis *et al.* 2000; Kamei *et al.* 2001; Birder *et al.* 2002; Walker *et al.* 2003; Karai *et al.* 2004; Iida *et al.* 2005; Jhaveri *et al.* 2005; Kanai *et al.* 2005; Christoph *et al.* 2006)
TRPV2	*TRPV2*	17p11.2 11 B2	Dystrophic patients and animal models	Increase in sarcolemma	Mechanosensation, Thermosensation	(Iwata *et al.* 2003)
TRPV3	*TRPV3*	17p13.3 11 B4	Deficient response to noxious and non-noxious heat; dermatitis and hairlessness	Knock-out/?		(Smith *et al.* 2002; Xu *et al.* 2002; Moqrich *et al.* 2005; Asakawa *et al.* 2006)
TRPV4	*TRPV4*	12q24.1 5 F	Hearing impairments, Abnormal thermal selection and osmotic regulation	Knock-out	Mechanosensation, Thermosensation	(Mizuno *et al.* 2003; Todaka *et al.* 2004; Lee *et al.* 2005; Tabuchi *et al.* 2005)
TRPV5	*TRPV5*	7q35	Hypercalciuria	Knock-out	Ca^{2+} reabsorbtion	(Hoenderop *et al.* 2003)
TRPA1	*TRPA1*	8q13 1 A3	Impaired cold, mechanical and chemical nociception	Antisense knockdown, Knock-out	Thermosensation, mechanosensation	(Story *et al.* 2003; Obata *et al.* 2005; Bautista *et al.* 2006; Katsura *et al.* 2006; Kim *et al* 2006;. Kwan *et al.* 2006)

Only the channels with confirmed involvement in human diseases or the channels whose mouse knock-out models show clear aberrant physiological function are listed. *Although TRPM5 is known to reside within a cluster of genes affected in BWS, no clear connection between BWS and TRPM5 up/down-regulation has been shown. ** *Krd* (kidney and retinal defects) mice have a deletion in the region containing *PKD2L1* gene and show kidney agenesis or cysts and retinal degeneration. TRPP3 is deleted in Krd mice.

of these diseases and the roles of the corresponding ion channels in maintaining normal cellular function.

To illustrate the broad physiological roles of TRP channels, Table 1 lists the physiological functions of TRP channels derived from genetic diseases, in *in vitro* experiments and from knock-out mice. Additional information on the biology, physiological functions and therapeutic potential of TRP channels can be found in several excellent recent reviews (Clapham, 2003; Nilius *et al.* 2005) and a series of reviews published in Cell Calcium (volume 33, issues 5–6, 2003) and Pflugers Archiv (volume 451, number 1, 2005).

Mucolipin 1 and MLIV

MLIV is a neurodegenerative disorder with an early onset. Patients with MLIV display severe psychomotor retardation and a developmental delay (reviewed in Bach, 2001; Slaugenhaupt, 2002). Other clinical manifestations of MLIV include achloridia and hypergastrinaemia (Schiffmann *et al.* 1998; Lubensky *et al.* 1999). At the cellular level, MLIV is a classic lysosomal storage disease with accumulation, in virtually all tissues and cells, of electron-dense vesicles and membranous inclusions containing phospholipids (Bach & Desnick, 1988; Bargal & Bach, 1989) and gangliosides (Zeigler & Bach, 1986). Proteolysis defects have not been shown in MLIV.

MLIV is caused by nonsense or missense mutations in the gene *MCOLN1*, which codes for TRP-ML1, a member of the TRP-ML subfamily (Bassi *et al.* 2000; Sun *et al.* 2000). The mutations result in deletion or affect cellular localization or ion selectivity and permeability of TRP-ML1 (LaPlante *et al.* 2004; Manzoni *et al.* 2004; Raychowdhury *et al.* 2004; Cantiello *et al.* 2005; Kiselyov *et al.* 2005).

TRP-ML1 is a lysosomal ion channel (Manzoni *et al.* 2004; Kiselyov *et al.* 2005; Miedel *et al.* 2006; Soyombo *et al.* 2006; Vergarajauregui & Puertollano, 2006), and is therefore expected to regulate lysosomal ion content, although its role in lysosomal function is still not known in full. TRP-ML1 was reported to be a Ca^{2+} channel (LaPlante *et al.* 2002, 2004), or an outwardly rectifying monovalent cation channel regulated by either Ca^{2+} (Cantiello *et al.* 2005) or pH (Raychowdhury *et al.* 2004). Our recent work shows that TRP-ML1 limits lysosomal acidification by providing a lysosomal H^+ leak pathway (Soyombo *et al.* 2006) (Fig. 1). H^+ is a critical lysosomal ion that regulates numerous lysosomal functions. The acidification

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of the lysosomal lumen is mediated by a vacuolar H^+ pump (Beyenbach & Wieczorek, 2006) and ClC family Cl^- channels (Jentsch *et al.* 2005). A H^+ leak mechanism that limits lysosomal acidification has been proposed but not identified. We suggest that in the absence of TRP-ML1 the lysosomes are chronically overacidified. In contrast with our findings, Bach *et al.* (1999) reported normal lysosomal pH in MLIV fibroblasts. The reason for the different findings is not known. However, we note that (a) we used two different techniques to estimate lysosomal pH, (b) MLIV cells are particularly sensitive to the weak base chloroquine (Goldin *et al.* 1999; Soyombo *et al.* 2006), which can only be if their lysosomes are more acidic than the normal lysosomes, (c) TRP-ML1 is permeable to H^+ and (d), the MLIV phenotype can be reversed by dissipating lysosomal pH (Soyombo *et al.* 2006).

TRP-ML1 has also been suggested to modulate lysosomal biogenesis by mediating fusion of lysosomes with late endosomes or fission of lysosomes from hybrid organelles (LaPlante *et al.* 2004; Piper & Luzio, 2004; Treusch *et al.* 2004). The biogenesis model integrates results obtained in human MLIV fibroblasts and in *C. elegans* deficient in the TRP-ML1 homologue CUP-5. An exchange between lysosomal and late endosomal content was reported to be affected in MLIV fibroblasts (LaPlante *et al.* 2002), which was taken to indicate that down-regulation of TRP-ML1 impedes the fusion of lysosomes with endosomes. On the other hand, the ablation of CUP-5 in *C. elegans* increased retention of lysosomal markers in late endosomes, which could be reversed by knocking-in the human TRP-ML1 (Treusch *et al.* 2004). This was interpreted as delayed reformation of lysosomes from the late endosomes in TRP-ML1-deficient cells and TRP-ML1 was suggested to promote the fission of lysosomes from late endosomes. Although an elegant hypothesis, several findings are not consistent with a primary role of TRP-ML1 in regulation of fusion/fission of endosomes/lysosomes. A primary role of TRP-ML1–membrane interaction events predicts that the loss of TRP-ML1 has to result in (a) accumulation of undigested lipids in *pre-lysosomal compartments* and (b) a marked change in the number of lysosomes (Fig. 2). Several reports, however, showed accumulation of lipids in the *lysosomes* of MLIV cells (Chen *et al.* 1998; Jansen *et al.* 2001; Soyombo *et al.* 2006), with no dramatic change in the lysosomal numbers (Treusch *et al.* 2004; Soyombo *et al.* 2006). It is likely that abnormal membrane trafficking in MLIV is secondary to accumulation of undigested material in these cells.

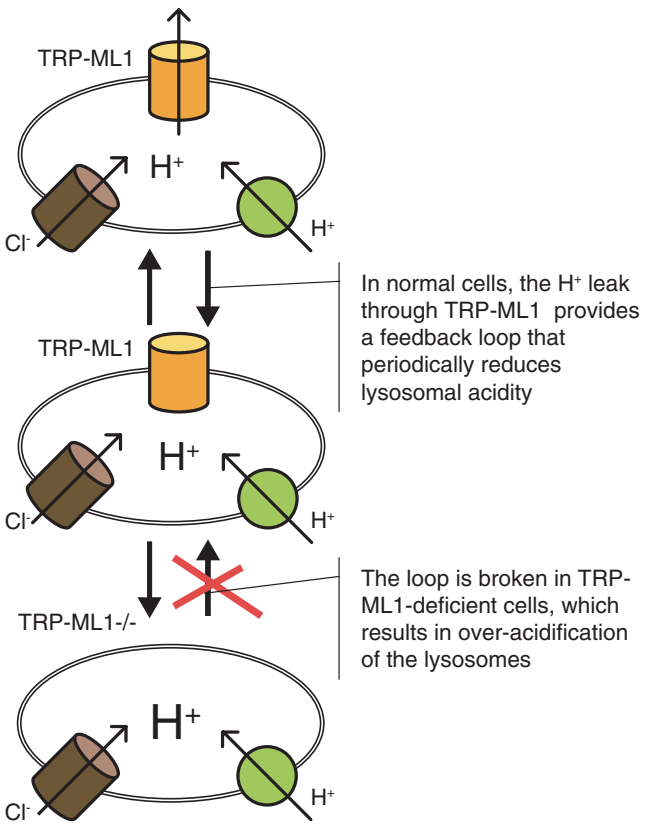

Figure 1. Function of TRP-ML1 as a lysosomal H^+ leak valve
Lysosomal acidification is mediated by V-type H^+ pumps and ClC Cl^- channels. At moderate lysosomal pH (top), TRP-ML1 provides a H^+ leak to limit lysosomal acidification. Cleavage of TRPML1 by a Cathapsin B-mediated mechanism leads to further acidification of the lysosomes (middle). Arrival of a new TRP-ML1 increases lysosomal H^+ leak to reestablish the moderate acidic state (top). The cycle is repeated resulting in oscillation in lysosomal pH between the moderate and acidic states. In the absence of TRP-ML1, the H^+ leak valve does not work, which results in chronically over-acidified lysosomes.

A particularly interesting aspect of TRP-ML1 physiology is its proteolytic cleavage in the lysosomes (Kiselyov *et al.* 2005; Miedel *et al.* 2006; Vergarajauregui & Puertollano, 2006). Since the full length TRP-ML1 seems to be the active form (Raychowdhury *et al.* 2004; Kiselyov *et al.* 2005), it is reasonable to propose that the cleavage is the major form of regulation of the channel. The full-length TRP-ML1 appears to be constitutively active (Raychowdhury *et al.* 2004; Kiselyov *et al.* 2005). The 'always-on' *modus operandi* of TRP-ML1 is consistent with its role in H^+ leak, or a shunt-like activity. Thus, the cleavage may be a mechanism to limit its activity to a selective subset of organelles in the lysosomal degradation pathway. The only other form of TRP-ML1 regulation discovered so far is by divalent ions (Cantiello *et al.* 2005; Soyombo *et al.* 2006), raising the possibility that changes in cytoplasmic Ca^{2+} ($[Ca^{2+}]_i$) during cell stimulation may acutely regulate channel activity.

Polycystin 2 and ADPKD

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited late onset renal disorder characterized by formation of kidney cysts leading to renal failure. ADPKD also has extrarenal effects that include formation

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of cysts in the pancreas, liver and spleen, hypertension and brain aneurisms. About 20% of the cases of ADPKD are associated with mutations in the gene *PKD2*, which codes for the ion channel polycystin 2 (TRPP2) (reviewed in Koptides & Deltas, 2000; Boucher & Sandford, 2004). TRPP2 physically interacts with polycystin 1 (PC1), which is probably involved in cell–cell communication and establishment of cellular junctions. Mutations in the gene coding for PC1 are responsible for the remaining cases of ADPKD.

TRPP2 is a cation channel with limited selectivity for Ca^{2+} (Gonzalez-Perrett *et al.* 2001; Koulen *et al.* 2002). Depending on cell type and expression system, TRPP2 localizes at the endoplasmic reticulum (Koulen *et al.* 2002), the primary cilia (Yoder *et al.* 2002; Nauli *et al.* 2003; Raychowdhury *et al.* 2005; Geng *et al.* 2006), the apical pole (Gonzalez-Perrett *et al.* 2001) or the basolateral surface of epithelial cells (Foggensteiner *et al.* 2000).

Why mutations in TRPP2 lead to formation of the fluid-filled kidney cysts is unclear. Localization of TRPP2 in the primary cilia led to a model in which TRPP2 reads the mechanical disturbance of the cilial apparatus in response to flow (Nauli *et al.* 2003; Ong & Wheatley, 2003; Nauli & Zhou, 2004). TRPP2 responds to mechanical stimulation (Montalbetti *et al.* 2005) and the association of TRPP2 with the cytoskeletal elements tropomyosin-1 (Li *et al.* 2003*a*), troponin I (Li *et al.* 2003*b*), α-actinin (Li *et al.* 2005*a*) and HS1-Associated Protein X1 (Hax-1) Gallagher *et al.* 2000) further supports the role of TRPP2 in mechanotransduction. The sensitivity of TRPP2 to mechanical stimuli is probably regulated by hormones, neurotransmitters and growth factors since stimulation of phospholipase C-coupled receptors activates TRPP2 (Ma *et al.* 2005).

The mechanotransduction model postulates that activation of TRPP2 by mechanical deflection of the cilia induces local Ca^{2+} influx, which propagates into the cell interior by Ca^{2+}-induced Ca^{2+} release through activation of ryanodine- and inositol (1,4,5) trisphosphate receptors (Nauli *et al.* 2003), or perhaps by activation of the endoplasmic reticulum resident TRPP2 (Koulen *et al.* 2002). The flow-induced Ca^{2+} responses in tubular epithelial cells mediated by TRPP2 are probably necessary for reporting changes in flow rate and fluid osmolarity. This can explain the particular susceptibility to ADPKD of the kidney, pancreatic and biliary duct and spleen, all of which experience large fluctuations in fluid flow and osmolarity.

How the TRPP2-mediated Ca^{2+} fluxes translate to the downstream cellular response has not been elucidated. The TRPP2-mediated Ca^{2+} fluxes probably have acute and long-term effects. The latter may include gene activation and regulation of cell proliferation.

TRPP2 was shown to be a cofactor in PC-1-dependent cell cycle arrest induced by activation of the JAK-STAT signalling pathway (Bhunia *et al.* 2002). Furthermore, the

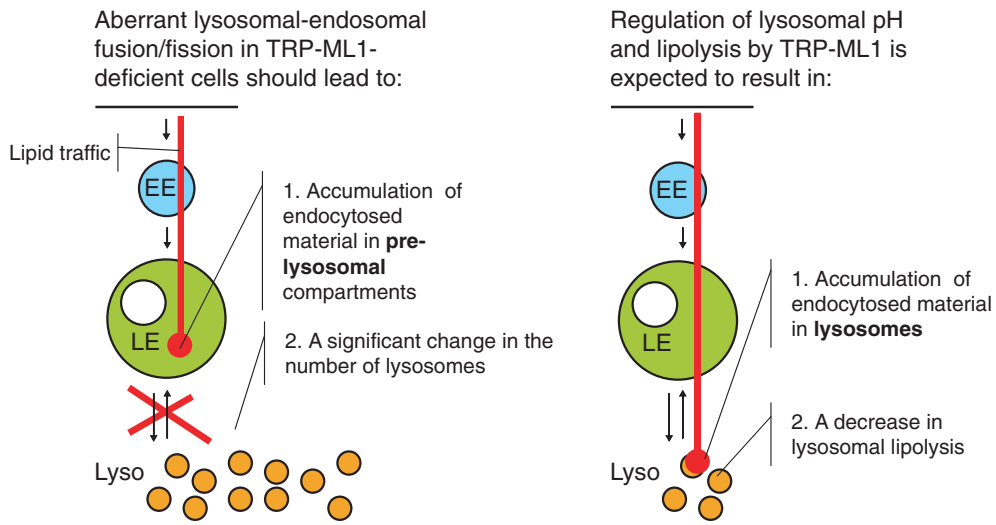

Figure 2. A comparison of the expected consequences of a role of TRP-ML1 in regulation of lysosomal biogenesis (left) or reduction in lysosomal acidity and hydrolytic activity (right)
The biogenesis model proposes that TRP-ML1 regulates fusion of lysosomes (Lyso) with late endosomes (LE) or reformation of lysosomes from hybrid organelles and their accumulation in the cytoplasmic pool. Consequently, in the absence of TRP-ML1 the exchange of endocytosed material between late endosomes and the cytoplasmic pool of lysosomes would be impaired and the endocytosed material would accumulate in late endosomes. This should lead to a significant change in the numbers of lysosomes. Regulation of lysosomal pH by TRP-ML1 leads to an alternative model in which lysosomal overacidification in the absence of TRP-ML1 affects lysosomal lipolysis and perhaps proteolysis. This model predicts accumulation of endocytosed material in lysosomes and a significant decrease in lysosomal hydrolytic activity.

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C terminus of TRPP2 binds the transcriptional suppressor Id2 (Li *et al.* 2005*b*), a member of an 'inhibitor of DNA binding' (Id) helix–loop–helix transcription factor subfamily. The Id family proteins lack DNA binding domains but they bind helix–loop–helix transcription factors, and inhibit their binding to DNA. Depending on cell type, this may inhibit or promote cell differentiation and proliferation (reviewed in Perk *et al.* 2005). In the absence of TRPP2 or PC1 most of Id2 is found in the nucleus. TRPP2 sequesters Id2 in the cytosol (Li *et al.* 2005*b*), which up-regulates a cyclin-dependent kinase (CDK) inhibitor p21 and down-regulates Cdk2. These findings suggest that the predominantly nuclear localization of Id2 in TRPP2- (or PC1-) deficient cells affects the p21-CDK cell cycle regulation cascade and results in aberrant cell growth (Li *et al.* 2005*b*). The role of TRPP2 Ca^{2+} transport function in either of these processes is unknown. Both effects, however, can account for the inverse relation between the levels of TRPP2 in kidney tissues and cell growth rates (Chang *et al.* 2006; Grimm *et al.* 2006).

Melastatin and cutaneous melanomas

A search for molecular correlates of the metastatic potential of human cutaneous melanomas has led to the identification of another TRP member, melastatin 1 (TRPM1). A loss of TRPM1 mRNA in metastasizing skin cancer is as robust a predictor of melanoma progression as any of the commonly accepted criteria (Duncan *et al.* 1998).

Normal and benign melanocytes express the full-length TRPM1 mRNA of approximately 5.4 kb along with some shorter products (Duncan *et al.* 1998; Fang & Setaluri, 2000). Metastatic melanomas and pigmented metastatic melanoma cell lines lack the full-length transcript, but express several short fragments of TRPM1 mRNA (Duncan *et al.* 1998; Fang & Setaluri, 2000). The anticancer drug hexamethylene bisacetamide (HMBA) reverses the loss of the full-length TRPM1 mRNA (Fang & Setaluri, 2000). Although the latter observation links melanoma progression to the loss of TRPM1, it does not establish a causative relation between the two.

TRPM1 mRNA levels in melanocytes and melanoma cell lines seem to depend on the melanocyte-specific transcription factor MITF as the TRPM1 promoter is under the MITF control and overexpression of MITF increases expression of TRPM1 (Miller *et al.* 2004; Zhiqi *et al.* 2004).

The channel properties and physiological function of TRPM1 have not been explored methodically. The only recording of TRPM1 activity was obtained with recombinant channel expressed in HEK 293 cells, where expression of the full-length TRPM1 dramatically increased resting $[Ca^{2+}]_i$ (Xu *et al.* 2001). When expressed alone, the full-length channel was targeted to the plasma membrane, while coexpression of the full-length and the short isoforms resulted in retainment of the full-length TRPM1 in the endoplasmic reticulum (Xu *et al.* 2001). It is currently unknown whether expression of TRPM1 in metastasizing lines inhibits their growth. The situation is further complicated by the fact that the native TRPM1 protein has not been identified and it was reported that normal melanocytes do not express noticeable levels of the predicted full-length TRPM1. A series of smaller products is detected instead, which was attributed to proteolysis of the full length protein (Zhiqi *et al.* 2004).

The properties and cellular localization of other TRP channels involved in cancer are somewhat better established. TRPC6 is a plasma membrane channel permeable to monovalent cations, modestly selective for Ca^{2+} and involved in Ca^{2+} influx induced by activation of G protein-coupled receptors (Estacion *et al.* 2004, 2006). TRPC6 was reported to be down-regulated in a murine autocrine tumour model (Buess *et al.* 1999) and to mediate the Ca^{2+} influx that maintains growth of prostate cancer epithelial cells (Thebault *et al.* 2006).

The highly Ca^{2+}-selective TRP channel, TRPV6, a vanilloid receptor homologue, is up-regulated in prostate cancer (Peng *et al.* 2001; Wissenbach *et al.* 2001, 2004; Fixemer *et al.* 2003; Schwarz *et al.* 2006) and in breast, thyroid, colon, and ovarian carcinomas (Zhuang *et al.* 2002). Chronic overexpression of TRPV6 reversibly increases proliferation of HEK 293 cells (Schwarz *et al.* 2006).

Another TRP channel associated with cancer is TRPM8. TRPM8 is a non-selective cation channel, that mediates cold sensation and response to menthol in neuronal cells (Peier *et al.* 2002) is also up-regulated in prostate cancer (Tsavaler *et al.* 2001; Fuessel *et al.* 2003; Henshall *et al.* 2003; Zhang & Barritt, 2006). Strikingly, TRPM8 seems to be lost at the very advanced stages of prostate cancer (Henshall *et al.* 2003). TRPM8 expression is regulated by androgen (Henshall *et al.* 2003; Zhang & Barritt, 2004; Bidaux *et al.* 2005) and is required for the survival of the androgen-sensitive LNCaP cell line (Zhang & Barritt, 2004).

Although a connection between apoptosis, cancer and $[Ca^{2+}]_i$ has been established, it is not clear why up- or down-regulation of these specific TRP channels induce cell transformation towards the cancerous phenotype. The remarkable plasticity of the cellular Ca^{2+} signalling machinery (Zhao *et al.* 2001) would probably allow the cells to adapt to a change in TRP channel activity in order to maintain normal Ca^{2+} signalling. It is likely that these TRP channels have a specific role in a regulatory protein complex in which they reside. For example, by colocalizing at the cell junctional complexes, TRP channels may participate in the regulation of cell adhesion and neighbour sensing. Studying the role of the

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cancer-associated TRP channels in their cellular context should test these possibilities.

TRPC6 and familial focal segmental glomerulosclerosis

Recent studies linked mutations in TRPC6 to familial focal segmental glomerulosclerosis (FSG), a form of nephropathy due to aberrant glomerular filtration (Reiser *et al.* 2005; Winn *et al.* 2005). FSG causes proteinuria, nephritic syndrome and a progressive loss of renal function, often resulting in end-stage renal disease (Daskalakis & Winn, 2006). Glomerular filtration is regulated by the slit diaphragm, which forms the renal filtration barrier. The glomerular podocytes with their foot processes are central component of the slit diaphragm (Somlo & Mundel, 2000). The podocytes are contractile cells that actively regulate glomerular permeability. Several structural proteins of podocytes participate in assembly or regulation of the slit diaphragm. Among them are nephrin, a 185 kDa single transmembrane spanning protein, localizing at signalling domains in the podocyte foot structure (Ruotsalainen *et al.* 1999) and podocin, a 42 kDa single transmembrane spanning protein that is found at the base of the podocyte foot structure (Roselli *et al.* 2002). Podocin interacts with nephrin and with a CD2-associated protein CD2AP (Schwarz *et al.* 2001). Mutations in these structural proteins and in α-actinin 4 (Mathis *et al.* 1998; Kaplan *et al.* 2000) have been linked to the familial forms of FSG. Mutations in *NPHS1* that codes for nephrin and in *NPHS2* that codes for podocin are responsible for the autosomal recessive forms of FSG (Kestila *et al.* 1998), whereas mutations in *ACTN4* coding for α-actinin 4 cause autosomal dominant form of FSG (Mathis *et al.* 1998).

Another autosomal dominant form of FSG was, unexpectedly, linked to mutations in TRPC6. In the glomerulus, TRPC6 is expressed at high levels in the podocyte foot structure, which determines glomerular permeability to macromolecules, including proteins. In the podocytes, TRPC6 interacts with nephrin and podocin, but not with CD2AP (Reiser *et al.* 2005; Winn *et al.* 2005). Mutations in TRPC6 associated with FSG were found in several cohorts and appear to fall into two categories: mutations that result in channel activation (Reiser *et al.* 2005; Winn *et al.* 2005), and mutations that had no apparent effect on channel activity (Reiser *et al.* 2005). The activating mutation P112Q was shown to increase the surface expression of TRPC6 (Reiser *et al.* 2005; Winn *et al.* 2005). The mechanism by which the R895C and E897K increase TRPC6 activity is not known.

It is possible that the activating mutations in TRPC6 result in an increased basal $[Ca^{2+}]_i$ to cause a tonic contraction of the podocytes and a persistent increase in glomerular permeability to macromolecules. The cause and effect for the mutations that do not increase TRPC6 activity is still to be determined. These mutations may boost TRPC6 sensitivity to stimulation, alter protein turnover or alter interaction with nephrin, podocin or with other TRPC channels. Podocytes express TRPC1, TRPC5 and TRPC6 (Reiser *et al.* 2005). TRPC6 function within a hetero-multimeric TRPC channels complex (Strubing *et al.* 2003; Bandyopadhyay *et al.* 2005; Dietrich *et al.* 2005*a*). It is thus possible that mutations that did not affect the activity of heterologously expressed TRPC6 may affect Ca^{2+} influx when TRPC6 is present in hetero-multimers.

It is unclear why some of the probands analysed by Reiser *et al.* were positive for such mutations, but did not show the kidney pathology (Reiser *et al.* 2005). The latter, and the lack of a clear kidney phenotype in the TRPC6 knock-out mice (Dietrich *et al.* 2005*b*), suggests that an unidentified genetic modifier is also involved in FSG pathogenesis. Indeed, it has been known since the 1970s that a circulating humoral factor is associated with FSG (Shalhoub, 1974). The involvement of a circulating factor was postulated based on the observations of recurrent proteinuria in transplant patients who were diagnosed with FSG (Ohta *et al.* 2001), induction of proteinuria in rats injected with serum from patients with FSG (Zimmerman, 1984) and remission of the proteinuria by removal of serum proteins by treatment with protein A–Sepharose (Dantal *et al.* 1994). It is possible that variations in the levels of the circulating factors between patients or with time may account for variability of manifestations of the disease and its timing among patients carrying mutations in TRPC6.

In conclusion, several human diseases highlight the key role that TRP channels play in cellular physiology. Tracing mutations in ion channels that are associated with human diseases provides an excellent tool to reveal their cellular function. Such studies can also identify the signalling pathway that interprets signals initialed by the ion channels in the specific cellular environment in which they function. An invaluable advantage of these systems is that they have very distinct phenotypes, which facilitates testing novel models and hypotheses.

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