

The Transient Receptor Potential Superfamily

Antibodies in Action

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The transient receptor potential (TRP) superfamily, one of the largest ion channel families, consists of a diverse group of proteins. The mammalian TRP superfamily comprises six subfamilies known as TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPML (mucolipins), TRPP (polycystin), and the TRPA (ANKTM1) ion channels. In mammals, approximately 28 genes encode the TRP ion channel subunits.¹⁻⁴ Due to their important roles in Ca²⁺ homeostasis, pain, and tumorigenesis, among others, TRP channels have lately been subjects of intensive research. Alomone Labs has developed antibodies against unique epitopes, intracellular as well as extracellular, of the TRP channels. The following article highlights the role that Alomone Labs antibodies play in the TRP research field.

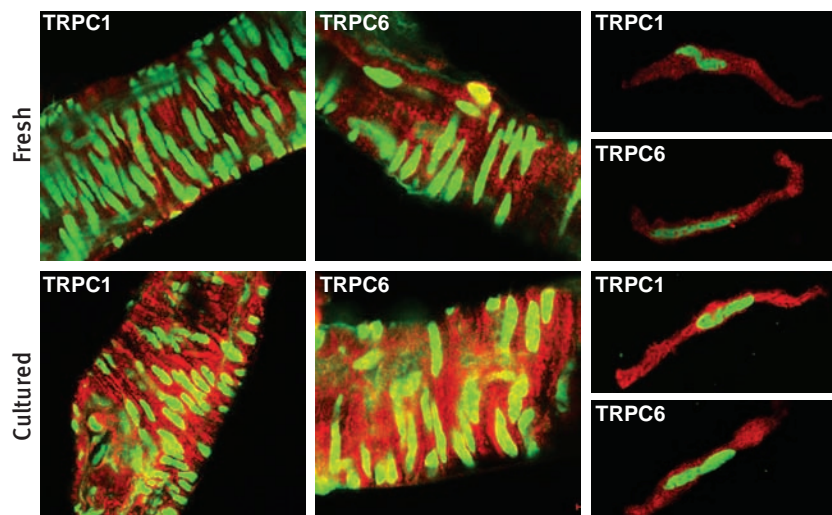
The TRP Superfamily

TRP channels have six putative transmembrane-spanning domains (TM) with a pore domain between the fifth and the sixth TM. Both the N- and the C-termini of TRPs are intracellular. All assemble as tetramers.³ TRP channels are widespread, and are either specifically or ubiquitously expressed in excitable and non-excitable cells.^{1,7} The selectivity of TRP channels varies widely between the different members of the family and with regard to different cations.⁵ TRP channels show diverse biophysical properties and gating mechanisms and play important roles in sensory physiology, being involved in almost every sensory signal initiation from pain sensation to the five senses. They are also major players in transepithelial Ca²⁺ and Mg²⁺ transport.

The TRPC Subfamily

The TRPC subfamily consists of seven proteins named TRPC1 to 7 which can be further divided into four subgroups based on their sequence homology and functional similarities: (1) TRPC1 (2) TRPC4 and TRPC5 (3) TRPC3, TRPC6 and TRPC7 (4) TRPC2.^{2,8} They are highly expressed in the central nervous system and to a lesser extent in peripheral tissues. TRPC1 was the first mammalian TRP protein that was reported to form an ion channel.^{2,9} It can co-assemble with other TRPC subunits (TRPC3, TRPC4, TRPC5)

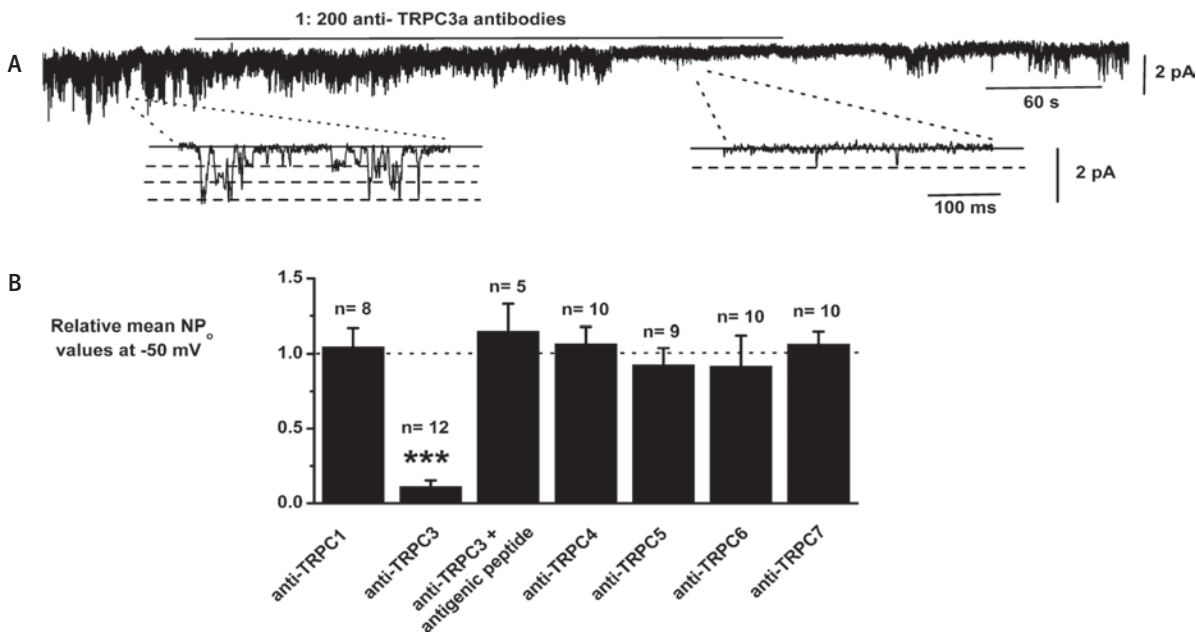
Expression of TRPC1 and TRPC6 in Rat Cerebral Arteries



Immunohistochemical and immunocytochemical staining of rat cerebral arteries using Anti-TRPC1 (#ACC-010) and Anti-TRPC6 (#ACC-017) antibodies. Immunofluorescent images showing TRPC1 staining (red) of the smooth muscle layer in whole mounts (*left*) and in single smooth muscle cells (*right*) from freshly dissected and cultured cerebral arteries. Stained smooth muscle cells are perpendicular to the longitudinal vessel direction. Note that single cells were isolated after the vessel had been cultured. Cells were costained with YOYO-1 (green).

Adapted from reference #16, with the kind permission of Dr. Hellstrand, P. of the division of Molecular and Cellular Physiology, Department of Physiological Sciences, Lund University, Lund, and the *Am. J. Physiol. Cell Physiol.*

Effect of Anti-TRPC Antibodies on Constitutively Active Cation Channel Activity in Inside-Out Patches



A, Bath application of, **Anti-TRPC3** antibody (#ACC-016) at 1:200 dilution reversibly inhibited constitutively active channel activity in patch held at -50 mV. Insets show individual channel currents on a faster time scale. B, mean data showing the effect of anti-TRPC antibodies: **Anti-TRPC1** (#ACC-010), **Anti-TRPC3** (#ACC-016), **Anti-TRPC4** (#ACC-018) **Anti-TRPC5** (#ACC-020) and **Anti-TRPC6** (#ACC-017) antibodies on constitutive channel activity represented as *NPs*. The data using anti-TRPC antibodies from different sources have been pooled; note that the anti-TRPC3a antibody had no effect on channel activity following preincubation with its antigenic peptide (***) $P < 0.001$. Adapted from reference #14 with the kind permission of Dr. Albert, A.P. of the Ion Channels and Cell Signalling Research Centre, Division of Basic Medical Sciences, St George's, University of London, Cranmer Terrace, London SW17 0RE, UK, and the *J. Physiol.*

to form heterotetramers whose properties are distinct from that of their homomeric form. The existence of the TRPC1 homomers has not been established as yet.¹⁻³ TRPC6 can form heterotetramers with TRPC3 and TRPC7. It is primarily expressed in brain, lung and muscle. High levels of expression of the channel were also found in human platelets. Recently it was reported that TRPC6 is also expressed in the kidney where a mutated channel has been implicated in kidney failure disease.^{10,11} The function and regulation of the TRPC ion channels remain elusive due to conflicting data and interpretations made by independent investigators.

Alomone's antibodies directed against the TRPC channels have been widely used for different applications, assessing expression and function of the TRPC channels.

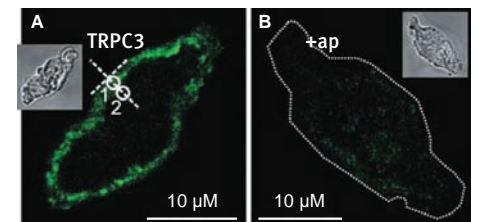
Expression of TRPC channels in brain, peripheral tissues and cell lines was demonstrated by different methods; western blotting, immunohistochemistry and immunocytochemistry using **Anti-TRPC1** (#ACC-010), **Anti-TRPC3** (#ACC-016), **Anti-TRPC4** (#ACC-018) and **Anti-TRPC6** (#ACC-017) antibodies.¹²⁻¹⁵ Expression of TRPC1 was also demonstrated by immunocytochemistry as well as western blotting in endothelium and smooth muscle of rat cerebral arteries.¹⁶

TRPC channels have been proposed to be involved in "Store Operated Calcium Entry" (SOCE). It was demonstrated that knockdown of TRPC3 by siRNA reduced SOCE by 64%. Knocking down TRPC3 expression was assessed by western blotting using Anti-TRPC3 antibody (#ACC-016).¹⁷ Anti-TRPC3 antibody was demonstrated to be functional by inhibiting constitutively active channel activity in inside-out patches.¹⁴ Reduction of Calcium entry in HUVECs was demonstrated using Anti-TRPC1 antibody (#ACC-010).¹⁸

Recently, the proteins comprising the Store Operated Calcium complex, the Orais (Orai1 and Orai2) and the STIMs (STIM1 and STIM2) were discovered.¹⁹ However TRPC1 is still considered to be part of this complex. Co-immunoprecipitation following western blotting using the **Anti-Orai1** antibody (#ACC-060) indicated that TRPC1, Orai1, and STIM1 concertedly generate SOC channels.²⁰

TRPC4 was shown to be necessary for neurite outgrowth in dorsal root ganglion. Its expression was increased after nerve injury and it was suggested to have an important role in sensory axonal regeneration.²¹ Immunohistochemical staining using the Anti-TRPC4 antibody have demonstrated the presence of TRPC4 in adult DRG neurons.²¹

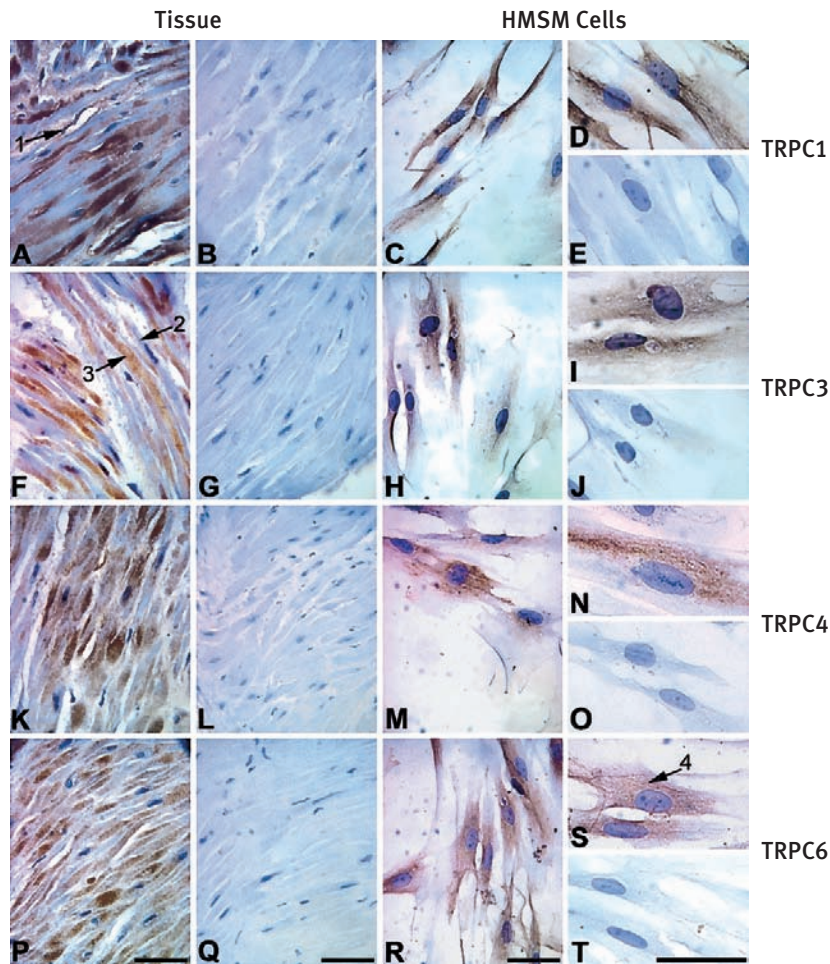
Expression of TRPC3 in Rabbit Ear Artery Myocytes



Immunocytochemical staining of TRPC3 channel proteins in rabbit ear artery myocytes using **Anti-TRPC3** antibody (#ACC-016). A, a single confocal plane fluorescence image of a myocyte labelled with anti-TRPC3a antibodies (1:200). B, another myocyte labelled with anti-TRPC3a antibodies (1:200) preincubated with their antigenic peptide (1:100). Insets in A and B show transmitted light image of these myocytes. White circles in A indicate Regions 1 and 2, which were used to analyse the localization of fluorescence. A dotted line was used in B to outline the contour of a cell, due to its low fluorescence.

Adapted from reference #14 with the kind permission of Dr. Albert, A.P. of the Ion Channels and Cell Signalling Research Centre, Division of Basic Medical Sciences, St George's, University of London, Cranmer Terrace, London SW17 0RE, UK, and the *J. Physiol.*

Expression of TRPC Channels in Human Myometrium

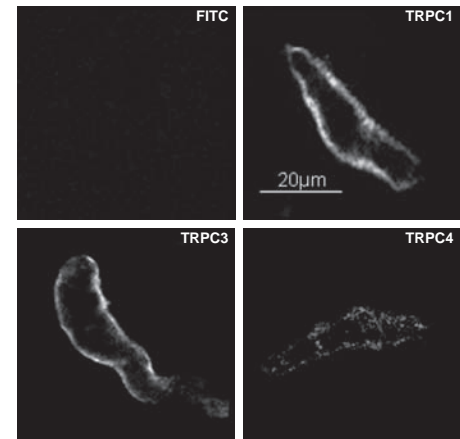


Immunohistochemical and immunocytochemical staining of term pregnant myometrial tissue and HMSM cells using Anti-TRPC3 (#ACC-016), Anti-TRPC4 (#ACC-018) and Anti-TRPC6 (#ACC-017) antibodies. Intense immunostaining of TRPC1, TRPC3, TRPC4 and TRPC6 was observed in human myometrial tissue sections (A, TRPC1; F, TRPC3; K, TRPC4; P, TRPC6) and primary cultured HMSM cells (C and D, TRPC1; H and I, TRPC3; M and N, TRPC4; R and S, TRPC6). No immunostaining was observed when human myometrial tissue sections and HMSM cells were incubated with pre-immune serum (B and E, TRPC1) or pre-absorbed primary antibodies (G and J, TRPC3; L and O, TRPC4; Q and T, TRPC6).

Arrow 1 = TRPC1 immunostaining in vascular tissue. Arrow 2 = limited immunostaining when nucleus is visible. Arrow 3 = intense immunostaining when the nucleus was not in the plane of focus. Arrow 4 = reticular staining in HMSM cells. Scale bars = 50 μ m.

Adapted from reference #15, with the kind permission of Dr. Tribe, R of the Parturition Research Group, Maternal and Fetal Research Unit, Department of Women's Health, 10th Floor North Wing, Guy's, King's and St Thomas' School of Medicine, St Thomas' Hospital Campus, Lambeth Palace Road, London SE1 7EH, and the *Mol. Hum. Reprod.*

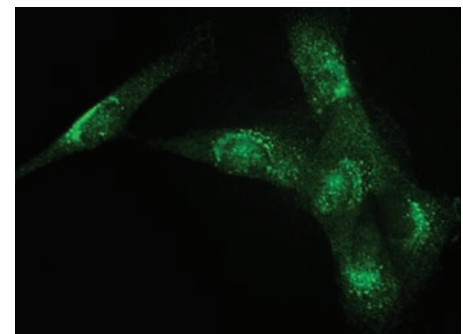
Expression of TRPC Channels in Guinea pig Gallbladder Smooth Muscle



Immunocytochemical staining of TRPC1 and TRPC3 in isolated guinea pig gallbladder smooth muscle (GBSM) layer using Anti-TRPC1 (#ACC-010) and Anti-TRPC3 (#ACC-016) antibodies. No immunofluorescence was evident when primary antibodies were omitted and only FITC-labeled secondary antibody was used.

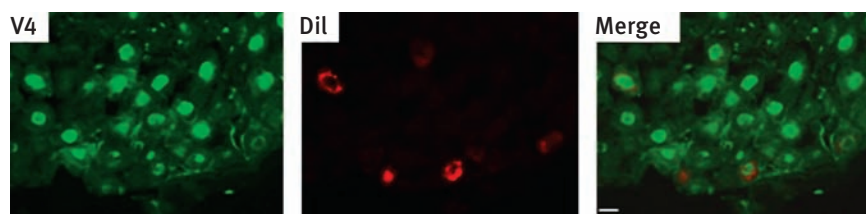
Adapted from reference #13, with the kind permission of Dr. Pozo, M.J. of the department of Physiology, University of Extremadura, Caceres, with the kind permission of *Am. J. Physiol. Cell. Physiol.*

Expression of TRPV4 in Human Synoviocytes



Immunocytochemical staining of human clonal SW982 synoviocytes using Anti-TRPV4 antibody (#ACC-034) (1:400). Staining was followed by Donkey anti-Rabbit FITC (1:200). The figure was reproduced with the kind permission of Ms. Abshire, S. and Dr. High, K. of the University of Kentucky Physiology, Lexington, KY, USA.

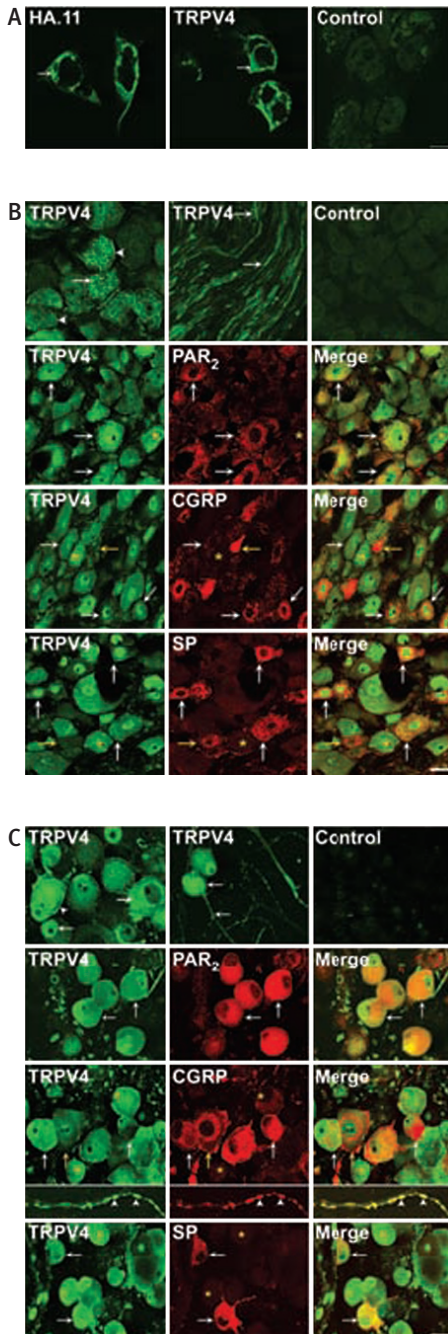
Expression of TRPV4 in Rat Vagal Pulmonary Sensory Neurons



Immunohistochemical staining of TRPV4 in rat vagal pulmonary sensory neurons using Anti-TRPV4 antibody (#ACC-034). The sections of nodose ganglion (8 μ m) were fixed and subject to immunohistochemistry for the TRPV4 channel. Left: immunoreactivity for TRPV4; middle: pulmonary sensory neurons as identified by Dil labeling; right: merge of the staining for TRPV4 and Dil.

Adapted from reference #55 with the kind permission of *Am. J. Physiol. Regul. Integr. Comp. Physiol.*

Localization and Expression of TRPV4 in HEK Cells and DRG Neurons



Immunocytochemical and immunohistochemical staining of TRPV4 in HEK cells and DRG neurons using **Anti-TRPV4** antibody (#ACC-034). A, localization of TRPV4 transiently expressed in HEK cells by immunofluorescence using antibodies to HA.11 epitope or TRPV4. Both antibodies detected immunoreactive TRPV4. Control shows preabsorption of TRPV4 antibody with antigen used for immunization. B, localization of immunoreactive TRPV4, PAR₂, CGRP or SP in sections of rat DRG. TRPV4 was detected in the soma at the plasma membrane and in intracellular locations, and also in fibres. C, Localization of immunoreactive TRPV4, PAR₂, CGRP or SP in rat DRG after 2 days in culture (for a detailed legend please refer to ref #30).

Adapted from reference #30, with the kind permission of *J. Physiol.*

The TRPV Subfamily

The TRPV subfamily is comprised of six members TRPV1-TRPV6. TRPV1-TRPV4 are thermosensitive ion channels while TRPV5 and TRPV6 function as epithelial Ca²⁺ channels. Each of the thermosensitive ion channels exhibits distinct thermal activation thresholds, ranging from noxious cold (<17°C) to noxious heat (>52°C).²²

The most established member of this family is the TRPV1 (previously also known as the capsaicin receptor or vanilloid receptor, VR1). Its involvement in thermal nociception has been well documented by different methods.²³ TRPV1 is expressed predominantly in nociceptors and in sensory neurons and is activated by moderate heat (≥43°C) and by capsaicin.²²⁻²⁴

Expression of TRPV1 in primary culture of trigeminal ganglion and in stably TRPV1-expressing neuroblastoma SH-SY5Y cells was demonstrated both by western blotting and by immunocytochemical staining using **Anti-TRPV1** antibody (#ACC-030).^{25,26}

The TRPV2 (VRL-1) however, has a higher threshold for activation by heat (≥52°C). It shares a 50% homology with TRPV1 but is not activated by capsaicin or by low pH.²⁷

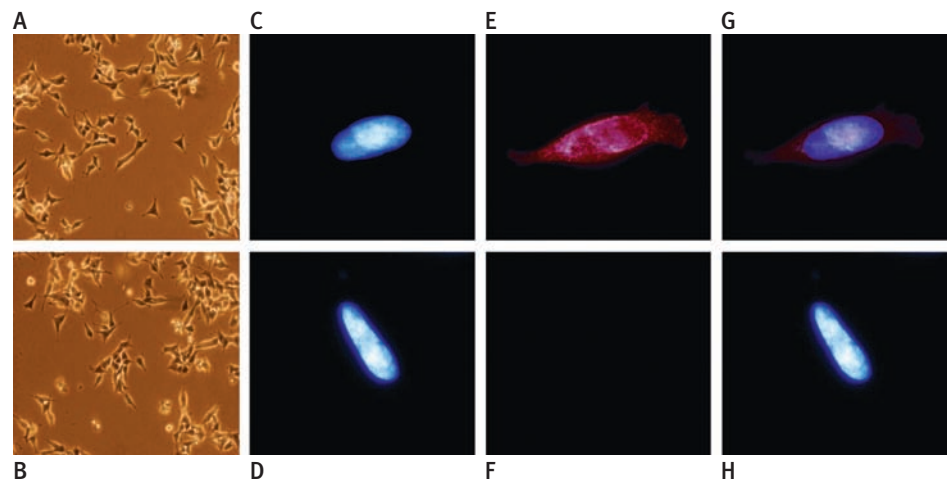
Both TRPV3 and TRPV4 are activated at a lower temperature threshold above 31°C and 25°C respectively. Both channels are expressed in

DRG. However, TRPV3 is also expressed in mouse keratinocytes but not in mouse DRG, while TRPV4 is expressed in a wide variety of tissues and may also have a possible role as mechanosensitive channel.^{28,29} TRPV4 (also named OTRPC4) is activated under hypotonic conditions and serves as an osmoreceptor. TRPV4 is expressed in brain, liver, kidney, heart, testis, dorsal root ganglion (DRG) and lung.⁶ Expression of the TRPV4 was demonstrated by the use of the **Anti-TRPV4** antibody (#ACC-034) in Western blotting, immunohistochemical and immunocytochemical staining.³⁰⁻³²

TRPV5 and TRPV6 form constitutively open channels, which are highly Ca²⁺ selective.^{33,34} TRPV5 is preferentially expressed in the kidney whereas TRPV6 is more prominently expressed in the intestine. TRPV6 is also expressed in human keratinocytes where it was shown to be necessary for keratinocyte differentiation. Its expression was up-regulated, both at the mRNA and protein levels following differentiation induced by 1,25-dihydroxyvitamin D₃. This up-regulation in expression was demonstrated using **Anti-TRPV6** antibody (#ACC-036) in Western blotting and immunohistochemical staining.³⁵

Although it is not expressed in benign prostate, TRPV6 was found to be upregulated in prostate cancer and correlation between expression and tumor grade was shown.^{36,37} In the prostate cancer cell line, LNCaP, direct involvement of TRPV6 in cell proliferation was demonstrated. Silencing

Expression of TRPV1 in Native and Stably TRPV1-Expressing SH-SY5Y Cells



Immunocytochemical staining of TRPV1 protein expression in native and stably TRPV1-expressing SH-SY5Y neuroblastoma cells using **Anti-TRPV1** antibody (#ACC-030). Phase contrast picture of TRPV1 cells (a) and native cells (b) showing identical morphology, 3200 magnification. Hoechst stained nucleus in TRPV1 cells (c) and native cells (d), immunization with primary TRPV1 antibodies and secondary goat anti-rabbit IgG antibodies conjugated to Alexa fluor red 568 in TRPV1 cells (e), and native cells (f) showing the TRPV1 expression in the cloned cells. (g and h) Superimposed images of c+e and d+f, respectively. Adapted from reference #25, with the kind permission of Dr. Lilja, J. of the department of Neurochemistry, Stockholm University, SE-106 91 Stockholm, Sweden and the *Toxicol. Sci.*

the TRPV6 gene lead to a decrease in the rate of LNCaP proliferation. Silencing of TRPV6 was assessed by the use of the Anti-TRPV6 antibody.³⁸

Both channels, TRPV5 and TRPV6 are also expressed in placenta, pancreas, salivary gland and colon.^{39,40}

The TRPM Subfamily

The TRPM family consist of eight members designated as TRPM1-8 that can be further divided into four pairs: TRPM1 and TRPM3; TRPM2 and TRPM8; TRPM4 and TRPM5; and TRPM6 and TRPM7.⁴¹ The family was named after the first member to be discovered, melastatin (TRPM1) whose gene was identified in metastatic and benign melanomas. TRPM channels have been suggested to play roles in tumorigenesis, proliferation, and differentiation. Recently, TRPM1 was found to be down-regulated in a highly metastatic line. The loss of TRPM1 expression has been reported to be correlated to melanoma aggressiveness.

TRPM7 and TRPM6 are involved in Mg²⁺ homeostasis and are unique among the TRP family members, possessing a functional kinase domain at their C-terminus.^{6,7} Although the kinase is not necessary for the function of the channel it may have a role in modulating the activation of the channel.⁷ Recent work demonstrated that TRPM7 is a critical mediator of anoxic cell death.^{42,43}

The TRPM8 is the cold (~28°C) and menthol receptor.² TRPM8 is expressed in dorsal root ganglia (DRGs) where about 5%-10% of the small diameter DRG neurons express the channel.^{44,45} In DRGs, TRPM8 expressing neurons do not express the TRPV1 channel.⁴⁶

Overexpression of TRPM8 was found in prostate cancer cells. However, the physiological and pathological roles that these cells play is still elusive.⁴⁰ In prostate, it was suggested that TRPM8 might play a possible role in the progression of cancer to the metastatic stage.⁴⁷

The TRPA Subfamily

The TRPA subfamily contains only one mammalian member, TRPA1.

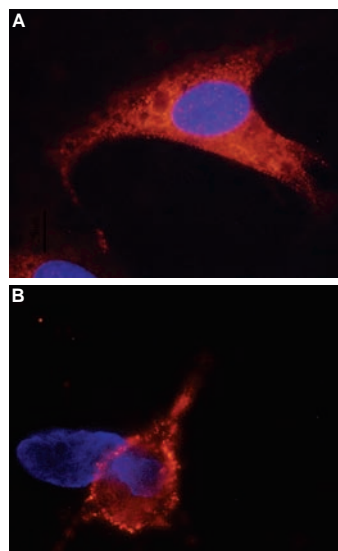
TRPA1 is expressed in hair cells and dorsal root ganglia (DRG). It was originally proposed to sense painfully cold temperatures, but a more conservative assessment is that it is sensitive to membrane/cytoskeletal perturbations by cold, plant compounds such as mustard oils and perhaps stretch.⁴⁸⁻⁵³ Recent study describes TRPA1 receptors on nerve fibres, urothelium, and interstitial cells. Co-localization of TRPA1 using **Anti-TRPA1 (extracellular)** antibody (#ACC-037) with TRPV1 and CGRP-positive nerve fibres in the

urothelium along with functional studies suggest a role for TRPA1 in afferent signals from the human outflow region and involvement of TRPA1 in efferent functions of the human urethra.⁵⁴

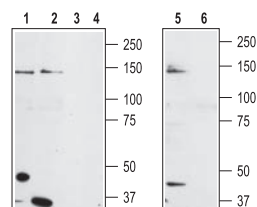
Due to their important roles in Ca²⁺ homeostasis, pain, and tumorigenesis, among others, TRP

channels have lately been subjects of intensive research. Alomone Labs has developed antibodies against unique epitopes, intracellular as well as extracellular, of the TRP channels. Antibodies from Alomone Labs have been widely cited in the literature for a variety of applications.

Expression of TRPM8 in Rat Dorsal Root Ganglion (DRG) Cells

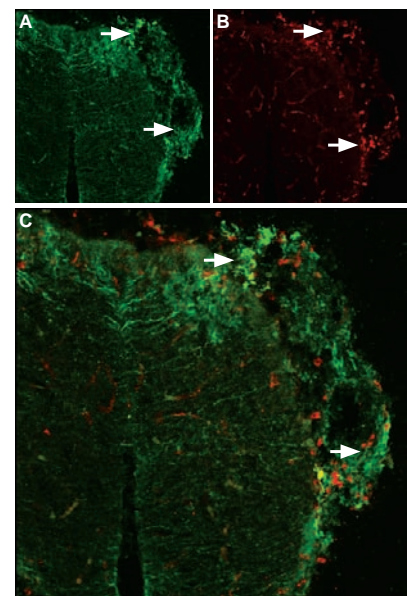


Immunocytochemical staining of TRPM8 in root dorsal root ganglion (DRG) cells. A. Intracellular staining of Paraformaldehyde-fixed and permeabilized DRG cells with **Anti-TRPM8 (extracellular)** antibody (#ACC-049), (1:500) followed by Alexa-555-conjugated goat-anti-rabbit secondary antibody. B. Extracellular staining of live DRG cells with **Anti-TRPM8 (extracellular)** antibody, (1:50) followed by Alexa-555-conjugated goat-anti-rabbit secondary antibody. The cell-permeable dye Hoechst 33342 (blue) was used for nuclear staining.

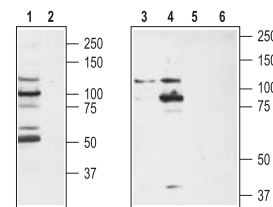


Western blot analysis of TRPM8 in prostate carcinoma cell lines; DU145 (lanes 1,3), LNCaP (lanes 2,4) and mouse-TRPM8 transfected HEK-293 (lanes 5,6) cell lines lysates: 1,2,5. **Anti-TRPM8 (extracellular)** antibody (#ACC-049), (1:200). 3,4,6. **Anti-TRPM8 (extracellular)** antibody, preincubated with the control peptide antigen.

Expression of TRPA1 in Mouse Dorsal Root Ganglia (DRG)

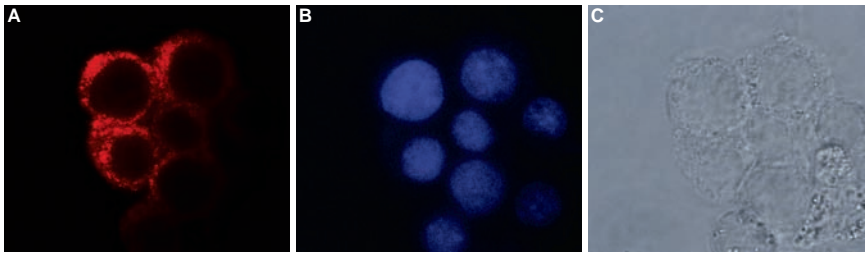


Immunohistochemical Staining of TRPA1 using **Anti-TRPA1 (extracellular)** antibody (#ACC-037) in mouse dorsal root ganglion (DRG) frozen section. A. TRPA1 (green) was distributed in patches (horizontal arrows). B. Neurons containing neurofilament 200 (red) also were distributed in patches. C. Confocal merge of TRPA1 and neurofilament 200 demonstrate partial overlap of these patches (arrows).



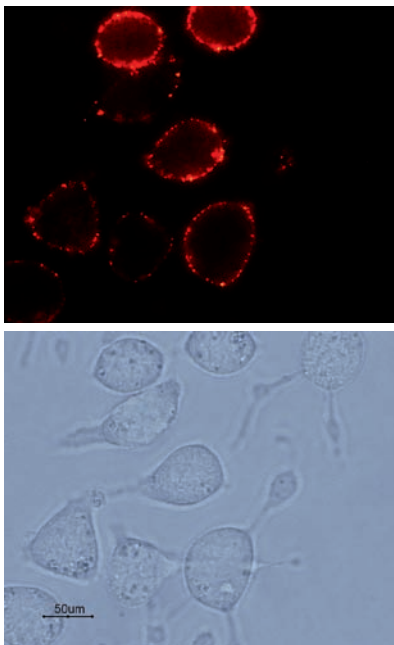
Western blot analysis of TRPA1 in rat DRG (lanes 1,2), non-differentiated PC12 cells (lanes 3,5) and differentiated PC12 cells (lanes 4,6) lysates: 1,3,4. **Anti-TRPA1 (extracellular)** antibody (#ACC-037), (1:200). 2,5,6. **Anti-TRPA1 (extracellular)** antibody, preincubated with the control peptide antigen.

Expression of TRPM7 in Rat GH3 Cell Line

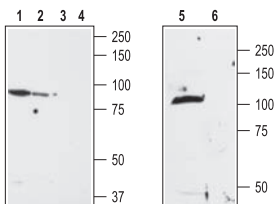


Immunocytochemical staining of TRPM7 in GH3 cells. A, GH3 cells stained with Anti-TRPM7 antibody (#ACC-047) (1:100), followed by goat-anti-rabbit-AlexaFluor-555 secondary antibody (red). B, Nuclear staining of GH3 cells with the cell permeable dye Hoechst 33342. C, Live intact GH3 cells.

Expression of TRPV2 in Rat Basophilic Leukemia Cells (RBL)



Immunocytochemical staining of RBL cells using Anti-TRPV2 (extracellular) antibody (#ACC-039) (1:100), followed by goat-anti-rabbit-Alexa fluor-550 (red) (x100).



Western blot analysis of ND7/23 cell line membrane (1,3), RBL lysates (2,4) and rat brain membrane (5,6): 1,2,5. Anti-TRPV2 (extracellular) antibody (#ACC-039), (1:200). 3,4,6. Anti-TRPV2 (extracellular) antibody, preincubated with the control peptide antigen.

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Related Products

Compound	Product #
Antibodies	
Anti-TRPC1	ACC-010
Anti-TRPC3	ACC-016
Anti-TRPC4	ACC-018
Anti-TRPC5	ACC-020
Anti-TRPC6	ACC-017
Anti-TRPV1	ACC-030
Anti-TRPV2	ACC-032
Anti-TRPV2 (extracellular)	ACC-039
Anti-TRPV3 (extracellular)	ACC-033
Anti-TRPV4	ACC-034
Anti-TRPV5	ACC-035
Anti-TRPV6	ACC-036
Anti-TRPA1 (extracellular)	ACC-037
Anti-Human TRPM1	ACC-041
Anti-TRPM7	ACC-047
Anti-TRPM8 (extracellular)	ACC-049
Anti-Human Orai1 (extracellular)	ACC-060
Anti-Orai2	ACC-061
Anti-STIM1 (extracellular)	ACC-063
Anti-STIM2	ACC-064
Anti-m1	AMR-001
Anti-m2	AMR-002
Anti-m3	AMR-006
Anti-P2Y1	APR-009
Anti-P2Y2	APR-010
Anti-P2Y4	APR-006
Anti-P2Y6	APR-011
Anti-P2Y11	APR-015
Anti-P2Y12	APR-012

Ca²⁺ Signaling Tool

Thapsigargin T-650

TRP Channel Modulators

5'-Iodoresiniferatoxin I-800
6'-Iodoresiniferatoxin I-805
Resiniferatoxin R-400