TRPC channels: An overview

L. Birnbaumer, Laboratory of Neurobiology, National Institute of Environmental Health Sciences, NIH, DHHS, 111 TW Alexander Drive, Research Triangle Park, NC 27709, USA. (Introduced by G. Housley)

In 1988 the 'transient receptor potential' or trp gene was cloned from *Drosophila*. This gene encoded an ion channel subunit that, in mutated form, was responsible for generating a transient receptor potential (rather than a sustained depolarization) of the compound eye. Molecular cloning of a Ca^{2+}-calmodulin- (CaCaM)-binding protein expressed in *Drosophila* eyes subsequently identified a close structural homologue, called trp-like. Both proteins were predicted to be membrane proteins that span the membrane six times with cytosolic N- and C-termini, no voltage sensor, but sequence similarity to voltage-gated channels. The subunits assemble as a tetramer to form non-selective cation channels with significant Ca^{2+} permeability. The first mammalian homolog of the TRP channesl – designated TRPC (for classical, or canonical) was cloned in 1995. There are now six subfamlies (C, V, M, P, ML and A) and 31 members, with a broad range of physiological functions, often associated with transduction of sensory signals. That said, TRPC channels are more enigmatic and their role has been linked with store-operated Ca^{2+} entry, and activation *via* a diverse range of modalities, including G protein-coupled receptor signaling, IP_3 receptor, and Ca^{2+}-calmodulin modulation. TRPC channel physiology is now being advanced with the support of transgenic models, revealing broad significance across domains as diverse as the regulation of intraluminal pressure-induced Bayliss effect and in the vagus-induced muscarinic receptor-dependent intestinal smooth muscle cell contraction. Vascular endothelial cell Ca^{2+} entry through TRPC leads to vascular smooth muscle relaxation. In non-excitable cells such as lung endothelial cells, Ca^{2+} entering through a TRPC contributes to the NFkB activation cascade and increases vascular permeability as seen in endotoxin induced lung injury. In platelets, Na^+ entering through TRPC channels promotes Ca^{2+} entry *via* Na^+-Ca^{2+} exchanger(s) critical in platelet activation and thrombus formation. In lymphocytes, Ca^{2+} entering through TRPC channels activates the CaCaM-activated phosphatase calcineurin (CaN) leading to dephosphorylation of phosphoNFATc, its translocation into the nucleus and activation of NFAT activated genes. In this last scenario, TRPCs are proinflammatory, in the cardiovascular system TRPCs are critical in blood pressure regulation and vascular tone, in the gut TRPCs are critical for normal intestinal transit. In a system akin to invertebrate visual transduction, the activation of melanopsin by light in intrinsically photosensitive retinal ganglion cells (ipRGCs) leads to activation of PLCbeta5 and two TRPC channel types. The ensuing depolarization is critical for entrainment of circadian rhythms in the supraoptic chiasmatic nucleus that receives afferents from the ipRGCs. A summary of TRPC roles is outlined in the Table. In the cochlea, TRPC channels contribute to regulation of sound transduction in the sensory hair cells.

Bair AM, Thippegowda PB, Freichel M, Cheng N, Ye RD, Vogel SM, Yu Y, Flockerzi V, Malik AB, Tiruppathi C. (2009) Ca^{2+} entry via TRPC channels is necessary for thrombin-induced NF-κB activation in endothelial cells through AMP-activated protein kinase and protein kinase Cδ. *Journal of Biological Chemistry* **284**: 563-74.

Davis J, Burr AR, Davis G, Birnbaumer L, Molkentin JD. (2012) A novel TRPC6-dependent pathway for myofibroblast transdifferentiation and wound healing in vivo. *Developmental Cell* **23**: 705-715.

Dietrich A, Mederos y Schnitzler M, Gollasch M, Gross V, Storch U, Dubrovska G, Obst M, Yildirim E, Salanova B, Kalwa H, Essin K, Pinkenburg O, Luft FC, Gudermann T, Birnbaumer L. (2005) Increased vascular smooth muscle contractility in *TRPC6*$^{-/-}$ mice. *Molecular and Cellular Biology* **25**: 6980-9.

Eckel J, Lavin PJ, Finch EA, Mukerji N, Burch J, Gbadegesin R, Wu G, Bowling B, Byrd A, Hall G, Sparks M, Zhang ZS, Homstad A, Barisoni L, Birbaumer L, Rosenberg P, Winn MP. (2001) TRPC6 enhances angiotensin II-induced albuminuria. *Journal of the American Society of Nephrology* **22**: 526-35.

Freichel M, Suh SH, Pfeifer A, Schweig U, Trost C, Weissgerber P, Biel M, Philipp S, Freise D, Droogmans G, Hofmann F, Flockerzi V, Nilius B. (2001) Lack of an endothelial store-operated Ca^{2+} current impairs agonist-dependent vasorelaxation in TRP4$^{-/-}$ mice. *Nature Cell Biology* **3**: 121-7.

Hartmann J, Dragicevic E, Adelsberger H, Henning HA, Sumser M, Abramowitz J, Blum R, Dietrich A, Freichel M, Flockerzi V, Birnbaumer L, Konnerth A. (2008) TRPC3 channels are required for synaptic transmission and motor coordination. *Neuron* **59**: 392-8.

Kim MS, Lee KP, Yang D, Shin DM, Abramowitz J, Kiyonaka S, Birnbaumer L, Mori Y, Muallem S. (2011) Genetic and pharmacologic inhibition of the Ca^{2+} influx channel TRPC3 protects secretory epithelia from Ca^{2+}-dependent toxicity. *Gastroenterology* **140**: 2107-15.

Klaiber M, Dankworth B, Kruse M, Hartmann M, Nikolaev VO, Yang RB, Völker K, Gassner B, Oberwinkler H, Feil R, Freichel M, Groschner K, Skryabin BV, Frantz S, Birnbaumer L, Pongs O, Kuhn M. (2011) A cardiac pathway of cyclic GMP-independent signaling of guanylyl cyclase A, the receptor for atrial

Examples of roles of TRPC channels (non-selective calcium-permeable cation channels) as seen from different points of view. Most of the roles were deduced from studying phenotypes developed in the corresponding knock-out mice or cells.

1.	**Mechanistic**	
	electrogenic coupling of GPCRs to voltage gated Ca^{2+} channels in excitable cells (*e.g.* Tsvilovskyy *et al.*, 2011)	All TRPCs
	direct Ca entry in excitable cells (*e.g.* Munsch *et al.*, 2003)	TRPC4
	direct Ca^{2+} entry in non-excitable cells (*e.g.* Tauseef *et al.*, 2012)	TRPC6
2.	**Biochemical**	
	NFAT activation – Calcineurin (CaN) activation by Ca-calmodulin (CaCaM) (Seth *et al.*, 2009; Poteser *et al.*, 2011)	TRPC1; TRPC3
	TLR4-CD14 signaling - MLCK (CaCaM) (Tauseef *et al.*, 2012)	TRPC6
	NFkB activation in endothelial cells (ECs)	
	– by GPCR - CaMKKβ (CaCaM) in ECs (Bair *et al.*, 2010)	TRPC4
	– by LPS - MLCK (CaCaM) MyD88-IRAK4-MLCK complex in ECs (Tauseef *et al.*, 2012)	TRPC6
	TNFα signaling - CaMKII (CaCaM) in monocytes (Smedlund *et al.*, 2010)	TRPC3
	CaN activation by CaCaM - NFAT (Poteser *et al.*, 2011)	TRPC3
	CaMKKIIβ-activation by CaCaM in activation of NFkB (Bair *et al.*, 2011)	TRPC4
	CaMKII activation by CaCaM - TNFα signaling - Ca-CaM-CaMKII (Tano & Vazquez, 2010)	TRPC3
	MLCK activation by CaCaM – activation of NFkB by LPS (Tauseef *et al.*, 2012)	TRPC6
	cGMP-indpendent signaling of the ANP receptorGC-A (/membrane guanylyl cylcase A) (Klaiber *et al.*, 2011)	TRPC3-C6
3.	**Physiological**	
	agonist-induced Ca mediated neurotransmitter release from dendrites (Munsch *et al.*, 2003)	TRPC4
	synaptic transmission and motor control; slow EPSCs (Hartmann *et al.*, 2008)	TRPC3
	neuronal afterdepolarization (Stroh *et al.*, 2012)	TRPC1-C4*
	plateau potentials in hippocampal CA1 pyramidal neurons (Tai *et al.*, 2010)	TRPC5
	control of vascular tone (Welsh *et al.*, 2003; Dietrich *et al.*, 2005)	TRPC6
	endothelial cell NO-EDRF (endothelium derived relaxing factor) generation - vascular smooth muscle relaxation (Freichel *et al.*, 2001)	TRPC4
	endothelial cell NO-independent EDH (endotheium dependent hyperpolarization- vascular smooth muscle relaxation (Senadheera *et al.*, 2012)	TRPC3
	endothelial cell migration - wound healing (lysoPC, fibroblast transdifferentiation) (Davis *et al.*, 2012)	TRPC6
	static stretch response of endothelial cells - stretch-ATR1-Gq-TRPC-Ca-ET1-ANP-GCA-cGMP-PKG-zyxin-gene transcription (Suresh Babu *et al.*, 2012)	TRPC3
	intestinal motility regulation by vagus (Tsvilovskyy *et al.*, 2009)	TRPC4+TRPC6
	cold transduction in the peripheral nervous system (Zimmermann *et al.*, 2011)	TRPC5
	exocrine secretion (saliva) (Liu *et al.*, 2007)	TRPC1
	efferocytosis and survival signaling in macrophages (Tano *et al.*, 2011)	TRPC3
	normal touch (Quick *et al.*, 2012)	TRPC3-C6*
	light entrainment by ipRGCs (melanopsin signaling) (Xue *et al.*, 2011)	TRPC6-C7*
	innate immunity (LPS) (Tauseef *et al.*, 2012)	TRPC6
	short term post synaptic memory - burst firing-induced after-depolarization (Phelan *et al.*, 2012)	TRPC1-C4*
	pheromone signal transduction in vomeronasal sensory neurons – lost in evolution between new world and old world monkeys and higher primates. (Liman & Innan, 2003)	TRPC2
4.	**In Disease (Pathophysiological)**	
	cardiac hypertrophy induced by Ang II (Onohara *et al.*, 2006)	TRPC3+TRPC6
	cardiac hypertrophy induced by transverse aorta constriction (TAC) (Seth *et al.*, 2009)	TRPC1
	albuminuria associated with Ang II induced cardiac hypertrophy (Eckel *et al.*, 2009)	TRPC6
	epileptogenic postsynaptic regenerative plateau potemtials (Phelan *et al.*, 2012)	TRPC1-C4*
	calcium toxicity in secretory epithelia (Kim *et al.*, 2011)	TRPC3
	neuronal excitotoxicity (Phelan *et al.*, 2012)	TRPC1-C4*
	neurotoxin induced ER stress response and ER calcium homeostasis (Selvaraj *et al.*, 2012)	TRPC1 loss
	pro-inflammatory in murine allergic asthma (Yildirim *et al.*, 2012)	TRPC1

* likely operating as obligatory heteromeric channels.

natriuretic peptide. *Proceedings of the National Academy of Sciences USA* **108**: 18500-5

Liu X, Cheng KT, Bandyopadhyay BC, Pani B, Dietrich A, Paria BC, Swaim WD, Beech D, Yildrim E, Singh BB, Birnbaumer L, Ambudkar IS. (2007) Attenuation of store-operated Ca^{2+} current impairs salivary gland fluid secretion in $TRPC1^{-/-}$ mice. *Proceedings of the National Academy of Sciences USA* **104**:

17542-7.
Munsch T, Freichel M, Flockerzi V, Pape HC. (2003) Contribution of transient receptor potential channels to the control of GABA release from dendrites. *Proceedings of the National Academy of Sciences USA* **100**: 16065-70.
Onohara N, Nishida M, Inoue R, Kobayashi H, Sumimoto H, Sato Y, Mori Y, Nagao T, Kurose H. (2006) TRPC3 and TRPC6 are essential for angiotensin II-induced cardiac hypertrophy. *EMBO Journal* **25**: 5305-16.
Liman ER, Innan H. (2003) Relaxed selective pressure on an essential component of pheromone transduction in primate evolution. *Proceedings of the National Academy of Sciences USA* **100**: 3328-32.
Phelan KD, Mock MM, Kretz O, Shwe UT, Kozhemyakin M, Greenfield LJ, Dietrich A, Birnbaumer L, Freichel M, Flockerzi V, Zheng F.(2012) Heteromeric canonical transient receptor potential 1 and 4 channels play a critical role in epileptiform burst firing and seizure-induced neurodegeneration. *Molecular Pharmacology* **81**: 384-92.
Poteser M, Schleifer H, Lichtenegger M, Schernthaner M, Stockner T, Kappe CO, Glasnov TN, Romanin C, Groschner K.(2011) PKC-dependent coupling of calcium permeation through transient receptor potential canonical 3 (TRPC3) to calcineurin signaling in HL-1 myocytes. *Proceedings of the National Academy of Sciences USA* **108**: 10556-61.
Quick K, Zhao J, Eijkelkamp N, Linley JE, Rugiero F, Cox JJ, Raouf R, Gringhuis M, Sexton JE, Abramowitz J, Taylor R, Forge A, Ashmore J, Kirkwood N, Kros CJ, Richardson GP, Freichel M, Flockerzi V, Birnbaumer L, Wood JN. (2012) TRPC3 and TRPC6 are essential for normal mechanotransduction in subsets of sensory neurons and cochlear hair cells. *Open Biology* **2**: 120068.
Selvaraj S, Sun Y, Watt JA, Wang S, Lei S, Birnbaumer L, Singh BB. (2012) Neurotoxin-induced ER stress in mouse dopaminergic neurons involves downregulation of TRPC1 and inhibition of AKT/mTOR signaling. *Journal of Clinical Investigation* **122**: 1354-67.
Senadheera S, Kim Y, Grayson TH, Toemoe S, Kochukov MY, Abramowitz J, Housley GD, Bertrand RL, Chadha PS, Bertrand PP, Murphy TV, Tare M, Birnbaumer L, Marrelli SP, Sandow SL. (2012) *Cardiovascular Research* **95**: 439-47.
Seth M, Zhang ZS, Mao L, Graham V, Burch J, Stiber J, Tsiokas L, Winn M, Abramowitz J, Rockman HA, Birnbaumer L, Rosenberg P.(2009) TRPC1 channels are critical for hypertrophic signaling in the heart. *Circulation Research* **105**: 1023-30.
Smedlund K, Tano JY, Vazquez G. (2010) The constitutive function of native TRPC3 channels modulates vascular cell adhesion molecule-1 expression in coronary endothelial cells through nuclear factor κB signaling. *Circulation Research* **106**: 1479-88.
Stroh O, Freichel M, Kretz O, Birnbaumer L, Hartmann J, Egger V. (2012) NMDA receptor-dependent synaptic activation of TRPC channels in olfactory bulb granule cells. *Journal of Neuroscience* **32**:5737-46.
Suresh Babu S, Wojtowicz A, Freichel M, Birnbaumer L, Hecker M, Cattaruzza M. (2012) Mechanism of stretch-induced activation of the mechanotransducer zyxin in vascular cells. *Science Signaling* in press.
Tai C, Hines DJ, Choi HB, MacVicar BA. (2011) Plasma membrane insertion of TRPC5 channels contributes to the cholinergic plateau potential in hippocampal CA1 pyramidal neurons. *Hippocampus* **21**: 958-67.
Tano JY, Smedlund K, Lee R, Abramowitz J, Birnbaumer L, Vazquez G. (2011) Impairment of survival signaling and efferocytosis in TRPC3-deficient macrophages. *Biochemical and Biophysical Research Communications* **410**: 643-7.
Tauseef M, Knezevic N, Chava KR, Smith M, Sukriti S, Gianaris S, Obukhov AG, Vogel SM, Schraufnagel SE, Dietrich A, Birnbaumer L, Malik AB, Mehta D. (2012) Cation channel TRPC6 activation of TLR4 in endothelial cells mediates sepsis-induced acute lung injury. *Journal of Experimental Medicine* doi: 10.1084/jem.20111355
Tsvilovskyy VV, Zholos AV, Aberle T, Philipp SE, Dietrich A, Zhu MX, Birnbaumer L, Freichel M, Flockerzi V. (2009) Deletion of TRPC4 and TRPC6 in mice impairs smooth muscle contraction and intestinal motility in vivo. *Gastroenterology* **137**: 1415-24.
Welsh DG, Morielli AD, Nelson MT, Brayden JE. (2003) Transient receptor potential channels regulate myogenic tone of resistance arteries. *Circulation Research* **90**:248-50.
Xue T, Do MT, Riccio A, Jiang Z, Hsieh J, Wang HC, Merbs SL, Welsbie DS, Yoshioka T, Weissgerber P, Stolz S, Flockerzi V, Freichel M, Simon MI, Clapham DE, Yau KW. (2011) Melanopsin signalling in mammalian iris and retina. *Nature* **479**: 67-73
Yildirim E, Carey MA, Card JW, Dietrich A, Flake GP, Zhang Y, Bradbury JA, Rebolloso Y, Germolec DR, Morgan DL, Zeldin DC, Birnbaumer L. (2012) Severely blunted allergen-induced pulmonary Th2 cell response and lung hyperresponsiveness in type 1 transient receptor potential channel-deficient mice.

American Journal of Physiology - Lung Cellular and Molecular Physiology **303**: L539-L549.
Zimmermann K, Lennerz JK, Hein A, Link AS, Kaczmarek JS, Delling M, Uysal S, Pfeifer JD, Riccio A, Clapham DE. (2011) Transient receptor potential cation channel, subfamily C, member 5 (TRPC5) is a cold-transducer in the peripheral nervous system. *Proceedings of the National Academy of Sciences USA* **108**: 18114-9.

Supported by the Intramural Research Program of the National Institutes of Health (project Z01-ES101684)