REVIEW

TRPC signaling mechanisms and therapeutic opportunities: Trapdoors are monitored by gatekeepers

Ammad Ahmad Farooqi[1]*, Asma M Riaz[2] and Shahzad Bhatti[3]
[1]Lab for Translational Oncology and Personalized Medicine, Rashid Latif Medical College (RLMC), 35 km Ferozepur Road, Lahore, Pakistan
[2]IMBB, The University of Lahore, Lahore, Punjab
[3]Department of Human Genetics and Molecular Biology, University of Health Sciences, Lahore, Pakistan

Abstract: This Review summarizes our current state of knowledge of the functional role of TRPC channels in health and disease, with particular emphasis on current advancements in the field. Additionally, this review provides an up-to-date summary of SKF-96365 acting on TRPC channels, and discusses strategies to further investigate the potential of these channels for therapeutic intervention.

Keywords: TRPC, SKF-96365.

INTRODUCTION

It is getting successively more noticeable that members of TRPC superfamily of cationic ion channels correspond to universal sensors, which convert multiple exogenous and endogenous chemical and physical stimuli into electrical and functional cellular responses. TRPCs have wide distribution in many different tissues. Phylogenetic categorization unfolds the fact that there are three major families of transient receptor potential channels. In line with this notion, TRPC or canonical TRP family, with seven members, TRPV family comprises six members and the TRPM family encompasses eight members. TRPM role in cellular activities might be found elsewhere (Ammad Farooqi *et al.*, 2011).

Although information on the functional importance of many of the TRPC proteins in signaling transduction cascades remains very limited, compelling evidence has accumulated for a pivotal role of TRPC in normal and pathological cellular activities.

TRPC1

Enhanced chemical influx and muscle degeneration are directly related to the lack of dystrophin in Duchenne muscular dystrophy (DMD) as well in the mdx mouse model of DMD. Transient receptor potential cation channels have been proposed as the probable candidates of Stretch-activated channels (SACs) which may possibly be in a direct involvement with the pathology of DMD. Investigation of transient receptor potential canonical channel 1 (TRPC1) levels and the streptomycin effects, as a SAC blocker, in muscles exhibited varied degrees of the dystrophic phenotype. Streptomycin physiologically reduced creatine kinase and inhibited the exercise-induced increases of total calcium in STN and diaphragm muscles. These different degrees of dystrophic phenotypes are possibly inferred to be due to different stretch-activated calcium channel protein TRPC1 levels (Matsumura *et al*., 2011).

The co-expression of TRPV4 and TRPC-1 in HEK293 cells resulted in an assembly type of 2V4:2C1. These heteromeric TRPV4-C1 channels exhibit quite distinct electrophysiological properties than those of homomeric TRPV-4 channels which are more sensitive towards extracellular Ca^{2+} inhibition (Ma *et al*., 2011).

No evidence as yet confirms that the mechanosensitivity of TRPC like current and ultimately the myogenic responsiveness of anterior cerebral arteries is in any case augmented by G(q/11)-coupled receptor activation (Anfinogenova *et al*., 2011). The expression of Transient receptor potential (TRP) C1 and C3 (TRPC1 and TRPC3) in vascular smooth musles is known and their involvement in vascular contractility has as well been speculated owing to the fact analyzed from RT-PCR and western blot analysis, that there is quite a greater smooth muscle depolarization, VDCC activation, and vascular contractility in the UTP (but not Phe) signaling pathway when the TRPC channel expression is altered in hypertension (Noorani *et al*., 2011). Transient Receptor Potential Canonical 1 (TRPC1) physiologically actively stimulates cardiovascular remodeling. The TRPC-1 transcripts are extensively sensitive to the NMD (nonsense-mediated decay) which when treated with cycloheximide, resulted in a cellular difference associated with NMD critical protein, up-frameshift-1 (UPF1).

Corresponding author: H ammadahmad638@yahoo.com

Thereof low UPF-1 expression is in part a factor causing inefficient clearance of aberrant transcripts and enhanced vascular smooth muscle cells proliferation (Dedman *et al*., 2011).

TRPC-1 has recently been reported as the probable candidate of SOCCs, despite the fact that its molecular components have not been categorically identified in all cell types. Interestingly, Bradykinin (BK), a mediator of pain and inflammation, activates SOCCSs and induces Ca(+2) mobilization into cytosol in human osteoblasts via the B(2) receptor. In line with this concept, pharmacological inhibition of TRPC channels repressed the effects of BK thus highlighting the notion that TRPC channels the decisive molecular components of SOCCs (Suzuki *et al*., 2011). The TRP protein is the target molecule of Ca^{2+} signaling in hCASMCs (Human coronary artery smooth muscle cells) elicited by SAA/LPC Serum amyloid A (SAA), an acute-phase protein, and lysophosphatidylcholine (LPC), and this target molecule appears to play role in coronary muscle dysfunction under pathophysiological and inflammatory conditions such as atherosclerosis (Tanaka *et al*., 2011). Accumulating evidence points towards the fact that microtubular machinery negatively regulates interaction between STIM1 and Orai1 or TRPC1 as verified by targeted inhibition of microtubules. Contrary to this, stabilization of the microtubules by paclitaxel impaired TG-evoked activation of SOCE and the interaction between STIM1 and the Ca(2+) channels Orai1 and TRPC1(Galán *et al*., 2011). Introduction of two TRP channel blockers SKF96365 and 2-APB, as well as flufenamic acid inhibits calcium influx in endocrine pituitary cells. According to the quantitative RT-PCR analysis the constitutively active cation channels (TRPC-1 in specific abundance) in pituitary cells are in turn stimulated via PKA contributing to indirect calcium signaling through a controlled pace-making depolarization i.e., in sodium dependent manner, while directly via the calcium conductance (Tomić *et al*., 2011). Escalating body of evidence suggests that signal transduction cascades trigger increment in intracellular calcium and depletion and refilling of the endoplasmic reticulum (ER) Ca^{2+} stores. In accordance with this observation, RNA interference studies represented that inhibition of TRPC1, STIM1 or ORAI1-ORAI3 mRNA can impede the rate of ER store refilling. (Murtazina *et al*., 2011).

TRPC3

In patients with chronic kidney disease, decreased extracellular calcium concentrations upregulate the expression of transient receptor potential canonical type 3 (TRPC3) channel protein in the chronic kidney disease patients. It is unknown whether extracellular calcium may regulate the expression of (TRPC3) channels in patients with chronic kidney disease Liu *et al*. (2011). The Structural studies indicated that distal C terminus (C2) domain and AMPK site of TRPC3 are responsive to Epo (erythropoietin) and indispensable for TRPC3 association with the cytoskeleton and an increase in the translocation and embedding of channel in plasma membrane in response to the stimulation of Epo (erythropoietin) which is an important signaling pathway controlling erythroid proliferation and differentiation Hirschler-Laszkiewicz *et al*., 2011. In vitro investigational studies unraveled the fact that treatment of TRPC3(+/+) macrophages with the pro-apoptotic cytokine TNFα induced time-dependent phosphorylation of IκBα, AKT and BAD, and this was considerably suppressed in TRPC3(-/-) macrophages. Compared to TRPC3 competent cells, TRPC3 deficient macrophages exhibited reduced constitutive cation influx, increased apoptosis and hampered efferocytosis (Tano *et al*., 2011).

WNK4 is a unique blood pressure modulator via TRPC3 mediated restriction of calcium influx. WNK4 mutants harboring the specific kinase-inactive mutation fail to mediate TRPC3 inhibition. This ultimately describes a previously un-defined role of WNK4 and as well reveals a therapeutic target unique enough i.e., for controlling the blood pressure in WNK4-related hypertension (Park *et al*., 2011).

There exists a dichotomy between TRPC-mediated Ca^{2+} signaling in the heart comprising two distinctive pathways that are linked differentially to gene transcription. The TRPC3 activity coupling to the translocation of NFAT (nuclear factor of activated T cells) into nucleus involves the microdomain Ca^{2+} signaling through the TRPC3 complexes which are triggered by PKC. TRPC3 is thereof a crucial signaling doorway in the Ca^{2+}-dependent control of cardiac gene expression (Poteser *et al*., 2011).

Confluence of information underlines an important correlation between TRPC3 upregulation and dilated cardiomyopathy (DCM), and thus TRPC3 inhibition comes out to be an effective therapeutic strategy for the prevention of DCM progression (Kitajima *et al*., 2011).

Transient receptor potential (canonical) channel (TRPC) 3 is a major channel for Ca2+ influx in salivary glands and pancreatic cells. This TRPC3-mediated Ca^{2+} influx functions to damage the pancreas and salivary glands. Patients with acute pancreatitis and Sjogren syndrome thus need to be treated via Pyr3 (highly selective pharmacological inhibitor of TRPC3 (Kim *et al*., 2011).

TRPC4

In human microvascular endothelial cells (HMEC-1)TRPC4 serves to stimulate the Ca^{+2} entry in a specific endothelial condition during the proliferating to a quiescent phenotype transition (Graziani *et al*., 2010).

TRPC-4 has recently been reported as the probable candidate of SOCCs, despite the fact that its molecular components have not been conclusively identified in all cell types.

TRPC-4, TNF-R1 and TNF-alpha Receptor Ubiquitous Signaling and Scaffolding protein (TRUSS) enhance the loading of Ca^{+2} of endoplasmic reticulum Ca^{+2} stores due to G-protein coupled m1 muscarinic acetylcholine receptor (m1AchR) stimulation. Thus highlighting the nascent insights into the connecting mechanism of TNF-R1 to GPCR-induced Ca^{2+} signaling in endothelial cells, resulting in trans endothelial permeability (Mace *et al*., 2010).

TRPC5

The (TRPC5) protein forms such calcium-permeable cationic channels which are stimulated by the agonists of G protein-coupled receptor. There is a potential involvement of lysophosphatidylcholine (LPC) and arachidonic acid generated by group 6 (GVI) phospholipase A2 (PLA2) enzymes in sphingosine-1-phosphate (S1P) evoked TRPC-5 activity (Al-Shawaf *et al*., 2011).

The regulation of TRPC5 is in way carried out via its direct phosphorylation by Gs/cAMP/PKA at positions S794 and S796. This mechanism holds its physiological importance in visceral tissues where β2-adrenergic receptor and muscarinic receptor are involved in the contraction and relaxation of smooth muscles (Sung *et al*., 2011).

The TRPC5 mRNA and its stability in endothelial cells was dose dependently increased by EPO. These findings suggest functionally upregulatedTRPC5 gene may ultimately be the one cause of hypertension induced by EPO in chronic kidney disease patients (Liu *et al*., 2011).

Rosiglitazone consists of such chemical moieties which modulate TRP channels strongly and independently of PPAR-γ, thus contributing to the agent's biological consequences and preparing the basis for novel pharmacology of TRP channel specifically the TRPC5. The wide expression of Transient receptor potential canonical 5 (TRPC5) channels in CNS potentiates fear responses. The native TRPC5-containing channel activity inhibition by progesterone which is majorly evoked by oxidized phospholipid opens up door for therapeutic strategies of TRPC-5 inhibition (Majeed *et al*., 2011a; Majeed *et al*., 2011b).

TRPC6

The upregulation of TRPC-6, TRPC-3 expression by Hypoxia-inducible factor-1 alpha (HIF-1α) leads to the development of cardiac hypertrophy in hypoxic stress. The mechanism involves the subsequent eliciting of TRPC current via upregulated TRPC-6 and TRPC-3, proceeding towards persistent and increased Ca^{2+}-calcineurin signals (Chu *et al*., 2011). TRPC-6, TRPC5, TRPC-3 and TRPC-7 function as the Ca^{+2} channels operated via endothelin type A receptor (ET(A)R). The activation of TRPC6 and TRPC3 mediated by ET(A)R requires the CIRB domain located at TRPC channel's C-terminus (Horinouchi *et al*., 2011).

The transient receptor potential canonical type 6 (TRPC6) channel mediated regulation of calcium influx is compulsory for the moncytes activity. The TRPC6 channel protein expression is upregulated in humans by the cysteine residues (Thilo *et al*., 2011). The PKA mediated phosphorylation of Ser(28) but not of Thr(69) negatively regulates TRPC6 (Horinouchi *et al*., 2011). The TRPC6 mediated Ca^{+2} entry attenuates and elucidates the injurious effects induced by albumins in chronic kidney diseases. The mechanism of attenuation involves the subsequent response of albumin overload, thus inducing ER stress and finally the apoptosis in podocytes i.e., the TRPC6 mediated Ca^{+2} entry Chen *et al*. (2011). Both the increased concentration of VEGF (Vascular endothelial growth factor) and transient receptor potential canonical type 6 (TRPC6) channels are coupled with proteinuric kidney diseases. Patient samples with diabetic nephropathy exhibit increased TRPC6 channel protein and VEGF receptor type 2 (VEGFR-2) protein in comparison to the control subjects Thilo *et al*., 2011. TRPC6 are the cation channels of plasma membrane. TRPC6 channels comprise a Zn^{2+} entry pathway, thereof signifying that they play a part in the Zn^{+2} homeostasis (Gibon ET *al*., 2011). Angoitensin-II regulates TRP6 in non-renal cells and the toxic effects of AngII on podocytes as well as its pathogenic role in glomerular disease result from an enhanced TRPC6 expression through a positive feedback signaling pathway of calcineurin/NFAT (Nuclear factor of activated T-cells) (Nijenhuis *et al*., 2011).

Increasing sophisticated information uncovered the fact that Ang II-induced contraction was largely dependent on Ca(2+) influx via receptor-operated cation channels. In conflict to the mechanism, Cilostazol specifically repressed diacylglycerol-activated TRPC channels through protein kinase A mediated phosphorylation of TRPC channels in HEK293 cells.The phosphorylation of TRPC6 at Thr69 is essential in regards to the therapeutic input of vasoconstriction i.e., the eliciting of vasorelaxant effects of phosphodiesterase (PDE) 3 inhibition against the Ang-II vasoconstrictive actions (Nishioka *et al*., 2011). The TRPC6 C-terminal calmodulin (CaM)- and inositol 1,4,5-trisphosphate receptors (IP(3)Rs)-binding (CIRB) site plays a significant physiological role in platelets via both, the Ca^{+2} entry modulation and ultimate aggregation through its CaM and IP(3)Rs interaction (Dionisio *et al*., 2011).

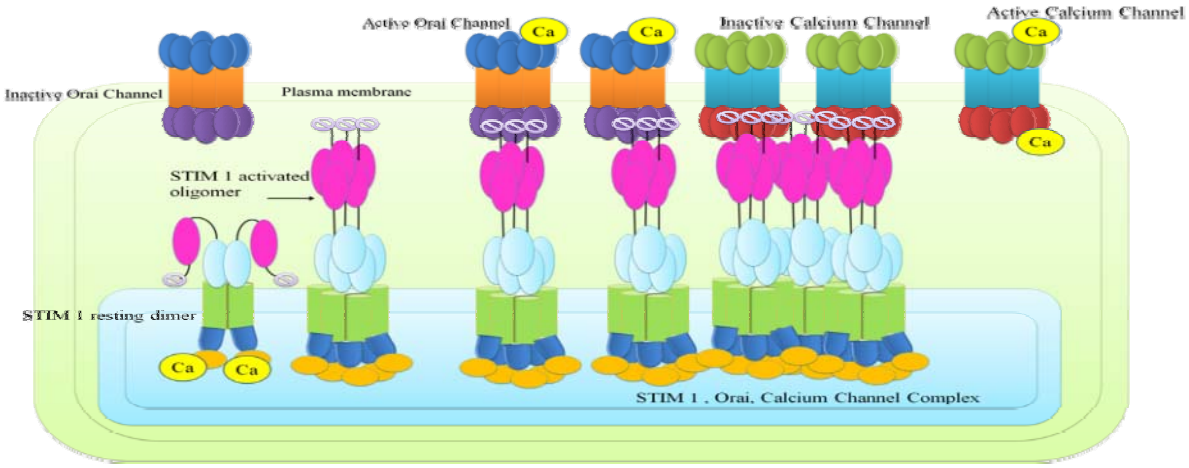

Fig: Illustration of molecular interaction of TRPC channels with multicomponent nanomachinery

SKF-96365

The Calcium receptor (CaR) stimulation in the adult rat cardiomyocytes induces TRP channel activation and further promotes the expression of TRPC3 but not that of TRPC1, which sustained the elevated [Ca^{2+}]. This elevated [Ca^{2+}] could however be reduced by the TRPC inhibitor SKF96365 (Feng *et al*., 2011). SKF96365 blocks the mast cell degranulation induced via TRPV2 activation. The reason being for this specific capability of inhibition, is that all three types of physical stimuli required for TRPV2 activation lead to the activation of SKF96365-sensitive current. SKF96365 could be used for treating excessive degranulation of mast cells (Zhang *et al*., 2011). SKF-96365 suppresses the Melittin (MEL)-induced activation of primary nociceptive cells which cause nociception and pain hypersensitivity. SKF-96364 serves both a therapeutic a s well a diagnostic tool in a way that via the inhibition it assures the involvement of TRPC channels in the pathology (Ding *et al*., 2011).

The widespread use of SKF96365 (SKF) as transient receptor potential canonical type (TRPC) channels blocker is put to a caution as there exist distinguished physiological and pathophysiological overlapping between low-voltage-activated (LVA) T-type calcium channels and TRPC channels. Therefore the interpretation of results considering SKF alone as a diagnostic tool in the native tissues for TRPC activity is doubted and needs to be revised (Singh *et al*., 2010).

SKF-96365 also called as the SOCC (store operated calcium channel) antagonist attenuates the basal increase in Ca^{+2} levels in pulmonary arterial smooth muscle cells caused by the upregulation of TRPC expression induced via BMP4 (bone morphogenetic protein 4). Thus the indirect attenuation of BMP4 by SKF-96365 ultimately prevents pulmonary vascular remodeling during pulmonary arterial hypertension (Lu *et al*., 2010).

SKF-96365 serves the therapeutic role in reducing the impact of HG on endothelial function. The endothelial dysfunction and vascular disease resulting from hyperglycemia, act by promoting the induction of prominent changes in TRPC1 expression which result in enhanced basal Ca^{2+} concentration. SKF-96365, the TRPC blocker inhibits this Ca^{+2} intake (Bishara *et al*., 2010). The calcium channel blockers SKF 96365 and 2-APB are used to prevent and elucidate the prothrombotic effects of carbon nanotubes (CNTs) Semberova *et al*. (2009). Apart from the TRPC5 pore blocking antibody SKF-96365 mediated blockade of the TRPC channels is a significant and novel therapeutic strategy for preventing the cytotoxicity and neurodevelopment impairment induced by mercury (Xu *et al*., 2011).

CONCLUSION

The abundance, distribution, sub-cellular localization, interaction networks and function of the transient receptor potential channels are in need of further comprehensive research before we transition to proteomics based diagnostics in personalized medicine.

REFERENCES

Al-Shawaf E, Tumova S, Naylor J, Majeed Y, Li J and Beech DJ (2011). GVI phospholipase A2 role in the stimulatory effect of sphingosine-1-phosphate on TRPC5 cationic channels. *Cell Calcium*, **50**(4): 343-350.

Farooqi AA, Javeed MK, Javed Z, Riaz AM, Mukhtar S, Minhaj S, Abbas S and Bhatti S (2011). TRPM

channels: same ballpark, different players, and different rules in immunogenetics. *Immunogenetics*. **63**(12): 773-787.

Anfinogenova Y, Brett SE, Walsh MP, Harraz OF and Welsh DG (2011). Do TRPC-like Currents and G-Protein Coupled Receptors Interact to Facilitate Myogenic Tone Development? *Am. J. Physiol. Heart Circ. Physiol.,* **301**(4): H1378-H1388.

Bishara NB and Ding H (2010). Glucose enhances expression of TRPC1 and calcium entry in endothelial cells. *Am. J. Physiol. Heart Circ. Physiol.,* **298**(1): H171-H178.

Chen S, He FF, Wang H, Fang Z, Shao N, Tian XJ, Liu JS, Zhu ZH, Wang YM, Wang S, Huang K and Zhang C (2011). Calcium entry via TRPC6 mediates albumin overload-induced endoplasmic reticulum stress and apoptosis in podocytes. *Cell Calcium,* **50**(6): 523-529.

Chu W, Wan L, Zhao D, Qu X, Cai F, Huo R, Wang N, Zhu J, Zhang C, Zheng F, Cai R, Dong D, Lu Y and Yang B (2011). Mild hypoxia induced cardiomyocyte hypertrophy via up-regulation of HIF-1α-mediated TRPC signaling. *J. Cell Mol. Med.,* doi: 10.1111/j.1582-4934.2011.01497.x.

Dedman AM, Majeed Y, Tumova S, Zeng F, Kumar B, Munsch C, Bateson AN, Wittmann J, Jäck HM, Porter KE and Beech DJ (2011). TRPC1 transcript variants, inefficient nonsense-mediated decay and low up-frameshift-1 in vascular smooth muscle cells. *BMC Mol. Biol.,***12**: 30.

Ding J, Xiao Y, Lu D, DU YR, Cui XY and Chen J (2011). Effects of SKF-96365, a TRPC inhibitor, on melittin-induced inward current and intracellular Ca2+ rise in primary sensory cells. *Neurosci. Bull.,* **27**(3): 135-142.

Dionisio N, Albarran L, Berna-Erro A, Hernandez-Cruz JM, Salido GM and Rosado JA (2011). Functional role of the calmodulin- and inositol 1,4,5-trisphosphate receptor-binding (CIRB) site of TRPC6 in human platelet activation. *Cell Signal.* **23**(11): 1850-1856

Feng SL, Sun MR, Li TT, Yin X, Xu CQ and Sun YH (2011). Activation of calcium-sensing receptor increases TRPC3 expression in rat cardiomyocytes. *Biochem. Biophys. Res. Commun.,* **406**(2): 278-284.

Galán C, Dionisio N, Smani T, Salido GM and Rosado JA (2011). The cytoskeleton plays a modulatory role in the association between STIM1 and the Ca^{2+} channel subunits Orai1 and TRPC1. *Biochem. Pharmacol.,* **82**(4): 400-410.

Gibon J, Tu P, Bohic S, Richaud P, Arnaud J, Zhu M, Boulay G and Bouron A (2011). The over-expression of TRPC6 channels in HEK-293 cells favours the intracellular accumulation of zinc. *Biochim. Biophys. Acta*. **1808**(12): 2807-2818.

Graziani A, Poteser M, Heupel WM, Schleifer H, Krenn M, Drenckhahn D, Romanin C, Baumgartner W and Groschner K (2010). Cell-cell contact formation governs Ca^{2+} signaling by TRPC4 in the vascular endothelium: Evidence for a regulatory TRPC4-beta-catenin interaction. *J. Biol. Chem.,* **285**(6): 4213-4223.

Hirschler-Laszkiewicz I, Tong Q, Waybill K, Conrad K, Keefer K, Zhang W, Chen SJ, Cheung JY and Miller BA (2011). The transient receptor potential (TRP) channel TRPC3 TRP domain and AMP-activated protein kinase binding site are required for TRPC3 activation by erythropoietin. *J. Biol. Chem.,* **286**(35): 30636-30646.

Horinouchi T, Higa T, Aoyagi H, Nishiya T, Terada K and Miwa S (2012). Adenylate cyclase-cAMP-protein kinase a signaling pathway inhibits endothelin type A receptor-operated Ca^{2+} entry mediated via TRPC6 channels. *J. Pharmacol. Exp. Ther.,* **340**(1):143-51.

Horinouchi T, Terada K, Higa T, Aoyagi H, Nishiya T, Suzuki H and Miwa S (2011). Function and regulation of endothelin type A receptor-operated transient receptor potential canonical channels. *J. Pharmacol. Sci.,* **117**(4): 295-306.

Kim MS, Lee KP, Yang D, Shin DM, Abramowitz J, Kiyonaka S, Birnbaumer L, Mori Y and Muallem S (2011). Genetic and pharmacologic inhibition of the Ca^{2+} influx channel TRPC3 protects secretory epithelia from Ca^{2+}-dependent toxicity. *Gastroenterology*, **140**(7): 2107-2115.

Kitajima N, Watanabe K, Morimoto S, Sato Y, Kiyonaka S, Hoshijima M, Ikeda Y, Nakaya M, Ide T, Mori Y, Kurose H and Nishida M. TRPC3-mediated Ca^{2+} influx contributes to Rac1-mediated production of reactive oxygen species in MLP-deficient mouse hearts. *Biochem. Biophys. Res. Commun.*, **409**(1): 108-113.

Liu Y, Krueger K, Hovsepian A, Tepel M and Thilo F. Calcium-dependent expression of transient receptor potential canonical type 3 channels in patients with chronic kidney disease. *Arch. Biochem. Biophys.,* **514**(1-2): 44-49.

Liu Y, Xu Y, Thilo F, Friis UG, Jensen BL, Scholze A, Zheng J and Tepel M (2011). Erythropoietin increases expression and function of transient receptor potential canonical 5 channels. *Hypertension,* **58**(2): 317-324.

Lu W, Ran P, Zhang D, Lai N, Zhong N and Wang J (2010). Bone morphogenetic protein 4 enhances canonical transient receptor potential expression, store-operated Ca^{2+} entry, and basal $[Ca^{2+}]i$ in rat distal pulmonary arterial smooth muscle cells. *Am. J. Physiol. Cell Physiol.,* **299**(6): C1370- C1378.

Ma X, Nilius B, Wong JW, Huang Y and Yao X (2011). Electrophysiological properties of heteromeric TRPV4-C1 channels. *Biochim. Biophys. Acta*. **1808**(12): 2789-2797.

Mace KE, Lussier MP, Boulay G, Terry-Powers JL, Parfrey H, Perraud AL and Riches DW (2010). TRUSS, TNF-R1, and TRPC ion channels synergistically reverse endoplasmic reticulum Ca^{2+} storage reduction in response to m1 muscarinic acetylcholine receptor signaling. *J. Cell Physiol.,* **225**(2): 444-453.

Majeed Y, Amer MS, Agarwal AK, McKeown L, Porter KE, O'Regan DJ, Naylor J, Fishwick CW, Muraki K and Beech DJ (2011). Stereo-selective inhibition of transient receptor potential TRPC5 cation channels by neuroactive steroids. *Br. J. Pharmacol.,* **162**(7): 1509-1520.

Majeed Y, Bahnasi Y, Seymour VA, Wilson LA, Milligan CJ, Agarwal AK, Sukumar P, Naylor J and Beech DJ (2011). Rapid and contrasting effects of rosiglitazone on transient receptor potential TRPM3 and TRPC5 channels. *Mol. Pharmacol.,* **79**(6): 1023-1030.

Matsumura CY, Taniguti AP, Pertille A, Santo Neto H and Marques MJ (2011). The stretch-activated calcium channel protein TRPC1 is correlated with the different degrees of the dystrophic phenotype in mdx mice. *Am. J. Physiol. Cell Physiol.,* **301**(6): C1344-C1350.

Murtazina DA, Chung D, Ulloa A, Bryan E, Galan HL and Sanborn BM (2011). TRPC1, STIM1, and ORAI influence signal-regulated intracellular and endoplasmic reticulum calcium dynamics in human myometrial cells. *Biol. Reprod.,* **85**(2): 315-326.

Nijenhuis T, Sloan AJ, Hoenderop JG, Flesche J, van Goor H, Kistler AD, Bakker M, Bindels RJ, de Boer RA, Möller CC, Hamming I, Navis G, Wetzels JF, Berden JH, Reiser J, Faul C and van der Vlag J (2011). Angiotensin II contributes to podocyte injury by increasing TRPC6 expression via an NFAT-mediated positive feedback signaling pathway. *Am. J. Pathol.,* **179**(4): 1719-1732.

Nishioka K, Nishida M, Ariyoshi M, Jian Z, Saiki S, Hirano M, Nakaya M, Sato Y, Kita S, Iwamoto T, Hirano K, Inoue R and Kurose H (2011). Cilostazol suppresses angiotensin II-induced vasoconstriction via protein kinase A-mediated phosphorylation of the transient receptor potential canonical 6 channel. *Arterioscler. Thromb. Vasc. Biol.*, **31**(10): 2278-2286.

Noorani MM, Noel RC and Marrelli SP (2011). Upregulated TRPC3 and downregulated TRPC1 channel expression during hypertension is associated with increased vascular contractility in rat. *Front Physiol.,* **2**: 42.

Park HW, Kim JY, Choi SK, Lee YH, Zeng W, Kim KH, Muallem S and Lee MG (2011). Serine-threonine kinase with-no-lysine 4 (WNK4) controls blood pressure via transient receptor potential canonical 3 (TRPC3) in the vasculature. *Proc. Natl. Acad. Sci.* USA. **108**(26): 10750-10755.

Poteser M, Schleifer H, Lichtenegger M, Schernthaner M, Stockner T, Kappe CO, Glasnov TN, Romanin C and Groschner K (2011). PKC-dependent coupling of calcium permeation through transient receptor potential canonical 3 (TRPC3) to calcineurin signaling in HL-1 myocytes. *Proc. Natl. Acad. Sci.* USA. **108**(26): 10556-10561

Semberova J, De Paoli Lacerda SH, Simakova O, Holada K, Gelderman MP and Simak J (2009). Carbon nanotubes activate blood platelets by inducing extracellular Ca^{2+} influx sensitive to calcium entry inhibitors. *Nano Lett.,* **9**(9): 3312-3317.

Singh A, Hildebrand ME, Garcia E and Snutch TP (2010). The transient receptor potential channel antagonist SKF96365 is a potent blocker of low-voltage-activated T-type calcium channels. *Br. J. Pharmacol.,* **160**(6): 1464-1475.

Sung TS, Jeon JP, Kim BJ, Hong CS, Kim SY, Kim J, Jeon JH, Kim HJ, Suh CK, Kim SJ and So I (2011). Molecular determinants of PKA-dependent inhibition of TRPC5 channel. *Am. J. Physiol. Cell Physiol.,* **301**(4): C823-C832.

Suzuki Y, Kodama D, Goto S and Togari A (2011). Involvement of TRP channels in the signal transduction of bradykinin in human osteoblasts. *Biochem. Biophys. Res. Commun.,* **410**(2): 317-321.

Tanaka T, Ikeda K, Yamamoto Y, Iida H, Kikuchi H, Morita T, Yamasoba T, Nagai R and Nakajima T (2011). Effects of serum amyloid a and lysophosphatidylcholine on intracellular calcium concentration in human coronary artery smooth muscle cells. *Int. Heart J.,* **52**(3): 185-193.

Tano JY, Smedlund K, Lee R, Abramowitz J, Birnbaumer L and Vazquez G (2011). Impairment of survival signaling and efferocytosis in TRPC3-deficient macrophages. *Biochem. Biophys. Res. Commun.,* **410**(3): 643-647.

Thilo F, Liu Y, Krueger K, Foerste N, Wittstock A, Scholze A and Tepel M (2012). Do cysteine residues regulate transient receptor potential canonical type 6 (TRPC6) channel protein expression? *Antioxid. Redox Signal*. **16**(5): 452-457.

Thilo F, Liu Y, Loddenkemper C, Schuelein R, Schmidt A, Yan Z, Zhu Z, Zakrzewicz A, Gollasch M and Tepel M (2011). VEGF regulates TRPC6 channels in podocytes. *Nephrol. Dial Transplant*, doi: 10.1093/ndt/gfr457

Tomić M, Kucka M, Kretschmannova K, Li S, Nesterova M, Stratakis CA and Stojilkovic SS (2011). Role of nonselective cation channels in spontaneous and protein kinase A-stimulated calcium signaling in pituitary cells. *Am. J. Physiol. Endocrinol. Metab.,* **301**(2): E370-E379.

Xu SZ, Zeng B, Daskoulidou N, Chen GL, Atkin SL and Lukhele B (2011). Activation of TRPC cationic channels by mercurial compounds confers the cytotoxicity of mercury exposure. *Toxicol. Sci.,* **125**(1): 56-68.

Zhang D, Spielmann A, Wang L, Ding G, Huang F, Gu Q and Schwarz W (2011). Mast-cell degranulation induced by physical stimuli involves the activation of Transient-Receptor-Potential Channel TRPV2. *Physiol. Res.,* PMID: 21574765.