TRPC Channels

Subjects: Cell Biology

Contributor: Tarik Smani Hajami

Transient receptor potential canonical (TRPC) channels are ubiquitously expressed in excitable and non-excitable cardiac cells where they sense and respond to a wide variety of physical and chemical stimuli. As other TRP channels, TRPC channels may form homo or heterotetrameric ion channels, and they can associate with other membrane receptors and ion channels to regulate intracellular calcium concentration. Dysfunctions of TRPC channels are involved in many types of cardiovascular diseases. Significant increase in the expression of different TRPC isoforms was observed in different animal models of heart infarcts and in vitro experimental models of ischemia and reperfusion. TRPC channel-mediated increase of the intracellular Ca2+ concentration seems to be required for the activation of the signaling pathway that plays minor roles in the healthy heart, but they are more relevant for cardiac responses to ischemia, such as the activation of different factors of transcription and cardiac hypertrophy, fibrosis, and angiogenesis.

Keywords: TRPC channel ; Ca2+ entry ; cardiac infarction ; cardiac repair

1. Introduction

The heart rate of a healthy adult ranges between 60 and 100 beats/min, which is mainly achieved by adequate function of the cardiac contraction/relaxation cycle. Adequate ventricular contraction is strongly dependent on effective excitation–contraction (EC) coupling in cardiac cells. Electrical stimuli travel across conducting cardiac tissues to the cardiomyocytes, inducing a cell-membrane depolarization activating ion channel and finally activating the cell contractile machinery (reviewed elsewhere [1][2]). EC coupling and cell contraction are critically dependent on Ca^{2+} influx and Ca^{2+} channel trafficking. The initial cell-membrane depolarization stimulates sarcolemma L-type Ca^{2+} channels, prompting a small influx of Ca^{2+} from the extracellular medium. Ca^{2+} entry triggers a large release of Ca^{2+} from the sarcoplasmic reticulum via ryanodine receptors (RyR), resulting in an increase in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$). The rise in $[Ca^{2+}]_i$ boosts Ca^{2+} binding to troponin C, which activates the contractile machinery. After contraction, $[Ca^{2+}]_i$ must decrease to allow cell relaxation, which is achieved mainly via two mechanisms: Ca^{2+} re-uptake by the sarco-endoplasmic reticulum Ca^{2+} ATPase (SERCA) pump and Ca^{2+} efflux by the sarcoplasmic Na^+/Ca^{2+} exchanger (NCX) [2][3]. Dysregulation of any of these Ca^{2+} handling processes is commonly associated with cardiac dysfunction.

Recently, other players emerged as key partners in the regulation of cardiac Ca^{2+} handling. Among these partners are the transient receptor potential (TRP) channels that are classified in a superfamily, including 28 mammalian TRP proteins divided according their genetic and functional homology into six families: TRPP (polycystin), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPML (mucolipin), and TRPC (canonical). TRP channels are composed of six transmembrane domains (TM1–TM6), with a preserved sequence called the “TRP domain” adjacent to the C-terminus of TM6 and a cation-permeable pore region formed by a loop between TM5 and TM6 (reviewed in Reference [4]). TRP channels are located in the plasma membrane, and their activation allows the entry of Ca^{2+} and/or Na^+, with higher permeability for Ca^{2+}. Although most TRP channels lack a voltage sensor, they can be activated by physical or biochemical changes, regulating Ca^{2+} dynamics by directly conducting Ca^{2+} or prompting Ca^{2+} entry secondary to membrane depolarization and modulation of voltage-gated Ca^{2+} channels [5]. The activation of different isoforms of TRP is associated with cell-membrane depolarization, for example, in smooth muscle cells [6][7] and in cardiac cells [8][9][10].

There is substantial evidence that TRP channels have important roles in mediating cardiac pathological processes, including cardiac hypertrophy and fibrosis [11][12][13], which all lead to deleterious cardiac remodeling and subsequent heart failure (HF). This review focuses on the role of TRPC channels and provides an overview of the most relevant and recent findings related to these channels and ischemia-related disease in the heart. Nevertheless, the activation mechanism of TRPC channels is not yet completely clarified, and even less so in cardiac cells. Previous studies using different cell types suggest that TRPCs can interact physically with different splice variants of the inositol triphosphate receptors (IP3R). For instance, TRPC1 [14], TRPC3 [15][16], and a splice variant of human TRPC4 [17] interact physically with the IP3R. Actually, it appears that IP3R and Ca^{2+}/calmodulin compete for a common binding site on TRPC3 since the displacement of

calmodulin by IP3R from the binding domain activates TRPC3 [18]. Others researchers proved that phosphatidylinositol 4,5-bisphosphate (PIP2) participates in the regulation of TRPC4 and TRPC5 [19][20]. $G\alpha_q$ protein also activates TRPC1/4 and TRPC1/5 through direct interaction [21]. Meanwhile, independent studies demonstrated that TRPC3, 6, and 7 are activated by diacylglycerol (DAG) [22][23][24][25]. Interestingly, TRPC4 and 5 channels also become sensitive to DAG when their interactions with other regulators are inhibited, such as protein kinase C (PKC) and Na^+/H^+ exchanger regulatory factor (NHERF) [26].

2. TRPC Channels in the Cardiovascular System

TRPC channels are classified into seven members (TRPC1–7) that are distributed based on biochemical and functional similarities into TRPC1/4/5, TRPC3/6/7, and TRPC2, which is a pseudogene in humans. The expression of TRPC isoforms in the heart was examined in different stages of animal development, animal models, and areas of the heart. They are expressed at very low levels in normal adult cardiac myocytes but their expression and activity might increase in pathological processes [12][13][27]. However, they likely display different patterns of expression in cardiac cells isolated from the sinoatrial node and in myocytes isolated from atrial or ventricular heart [22][28]. In human cardiac tissues and/or neonatal rat cardiomyocytes, messenger RNA (mRNA) of TRPC5 [29][30] and TRPC6 [31] was detected. In animal models, the expression of TRPC1/3–7 was confirmed in adult rat and mouse ventricle and atrial cardiac myocytes either at mRNA or protein levels [13][32][33]. Other reports showed that TRPC1/3–6 are expressed in rat ventricular myocytes of fetal and neonatal ventricular myocytes [28][34]. In sinoatrial node cells, TRPC1, 2, 3, 4, 6, and 7 mRNA expression levels are detected using RT-qPCR, whereas TRPC5 expression is not observed. Furthermore, experiments using immunohistochemistry confirmed protein expression of TRPC1, 3, 4, and 6, but not TRPC7 in mouse sinoatrial node and in isolated pacemaker cells [35]. In the case of cardiac fibroblasts, all TRPC isoforms were described. In particular, the mRNAs of TRPC1, 3, 4, and 6 are detected in mouse cardiac fibroblasts. Meanwhile, isolated rat ventricular fibroblasts have significant mRNA expression of TRPC2, 3, and 5 [36][37][38]. Experiments using immunocytochemistry and Western blot also revealed the expression of TRPC1, 3, 4, and 6 proteins in rat and human cardiac fibroblasts [39][40][41].

A functional TRPC channel is composed of four proteins, allowing it to form homo or heterotetramers [42]. However, the concept of TRPC multimerization was barely addressed in cardiac myocytes. A previous study from Molkentin's group suggested multimerization of TRPC3 and homotypic TRPC6 in adult mouse cardiac myocytes since they demonstrated, using an immunoprecipitation approach, that TRPC3 can associate with TRPC4 protein [5]. More recently, TRPC6 was suggested to form a heteromeric complex with TRPC3 and nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase 2 (NOX2) protein in diabetic mouse heart. Nonetheless, this study used HEK293 cells to confirm the interaction between TRPC3 and TRPC6 by immunoprecipitation [43]. It should be noted that other studies indicated that TRPC channels can form a macromolecule complex with the NCX [44], Na^+/K^+ pump [45], and SERCA pump [46]. Therefore, they might create a microenvironment facilitating the fine-tuning of Ca^{2+} homeostasis and excitation–contraction coupling (reviewed elsewhere [47][48][49]). In fact, recent evidence confirmed that TRPC3 mediates Ca^{2+} and Na^+ entry in proximity of NCX, elevating Ca^{2+} levels and cardiac contractility [44]. Certainly, more precise investigations about TRPC heteromerization will be welcome to reveal whether this concept is similar to that observed in other cells such as smooth muscle cell [50], platelets [51], hippocampus [52], or rat brain [53]. Actually, Bröker-Lai J et al. [52] combined quantitative high-resolution mass spectrometry with affinity purifications using isoform-specific antibodies on membrane fractions prepared from wild-type (WT) and target-knockout (KO) brains to demonstrate that TRPC1, 4, and 5 form heteromeric complexes in the brain, particularly in the hippocampus.

3. Role of TRPC Channels in Cardiac Ischemia

3.1. TRPC Channels in Myocardial Infarction

One of the first pieces of evidence of the participation of TRPC in myocardial infarction (MI) was proposed using bioinformatic analysis combined with experimental approaches. Zhou et al. [54] demonstrated an increase in the expression of TRPC6, which was experimentally validated in a one-month post-MI rat model, suggesting TRPC6 as a potential therapeutic target for MI. Later, other studies highlighted the induction of TRPC proteins under MI and explored the idea that Ca^{2+} influx through TRPC channels overexpressed after MI contributes to cardiac dysfunction and adverse remodeling. In fact, significant increases in TRPC1, 3, 4, and 6 mRNA levels in mice one, two, and six weeks post MI were observed, as compared with sham [55]. This channel upregulation correlates with the increase in Ca^{2+} entry when myocytes isolated from MI adult mouse are stimulated with cyclopiazonic acid and OAG. Furthermore, mice expressing dn-TRPC4 have less pathological hypertrophy, better cardiac hemodynamic performance, and increased survival after MI, as compared with WT mice [55]. Therefore, the loss of TRPC4 function likely protects against the progression of cardiac dysfunction after MI. Interestingly, Jung et al. [56] suggested that gain of function of TRPC4 due to a genetic variation

(I957V) causes an increase in channel activity, which has a protective effect against MI. The authors identified a single-nucleotide polymorphism (SNP) in TRPC4 that associates with MI risk in a case–control study. They further used multivariate analysis to show a protective effect of the I957V allele against MI risk, but only in diabetic patients. Therefore, the mutated TRPC4-I957V is thought to mediate higher Ca^{2+} signals, perhaps to facilitate the generation of endothelium and nitric oxide-dependent vasorelaxation. Nevertheless, the authors did not experimentally test this hypothesis. Recently, we observed significant dysregulation in the expression of several TRPC isoforms in a Wistar rat model of MI induced by transient ligation of the left coronary artery. A PCR-based micro-array, qRT-PCR, and Western blotting demonstrated significant upregulation of TRPC1, 3, 4, 5, and 6, whether in at-risk or in remote zones of infarcted hearts, as compared to sham. Specific downregulation of TRPC5 in MI rats infused with urocortin-2 at the onset of reperfusion was observed, offering a role of TRPC5 in cardioprotection [13].

In the case of TRPC3 and 6, a previous study determined that TRPC6 KO mice had significantly higher rates of mortality due to ventricular wall rupture throughout 3–7 days post MI [37]. In contrast, TRPC3/6/7 triple-KO mice subjected to transient MI (30 min of ischemia followed by 24 h reperfusion) exhibit reduced infarct size, better cardiac performance, and less cardiac tissue damage post MI, as compared with WT animals. In addition, they have reduced apoptosis through the inhibition of the calcineurin–nuclear factor of activated T cells (NFAT) signaling pathway [24]. These results suggest that TRPC3, 6, and 7 contribute significantly to worsening MI impacts on cardiac function. Further investigations will be welcome to clarify the discrepancy between these KO studies. It will be interesting to examine whether the cardioprotective effects observed in the triple-KO mice affect the transformation of myofibroblasts required during wound healing and scar formation.

3.2. TRPC Channel Role in Ischemia and Reperfusion Injuries and Cardioprotection

Ischemia and reperfusion (I/R) injury is the main cause of cell apoptosis and necrosis observed after an MI. Several studies demonstrated evidence linking cytosolic Ca^{2+} increase through TRPC and apoptosis after I/R [24][57]. Studies using TRPC inhibitors examined their role in I/R injuries. For instance, Kojima et al. [58] showed, in a Langendorff-perfused mouse heart under I/R, that left-ventricular functions are significantly improved by the administration of ion channel blockers (2-aminoethoxydiphenyl borate (APB) and La^{3+}) during the initial 5 min of reperfusion, suggesting a TRPC channel role in contractile dysfunction in reperfused ischemic myocardium. In an atrial cardiac cell line, H9C2, the addition of SKF96365, another widely used inhibitor of TRPC, ameliorates injuries induced by hypoxia–reoxygenation (H/R) [24]. However, it is well known that 2-APB and La^{3+}, as reviewed previously [59][60], as well as SKF96365 [59][60], are not specific to TRPC channels and may block other cationic channels. Therefore, these results should be supported by experiments using siRNA and/or TRPC-deficient mice. Actually, other reports used different molecular approaches to identify TRPC isoforms responsible for Ca^{2+} entry and its relationship with cardiac myocyte death under I/R. For example, Shan et al. [57] observed that transgenic mice overexpressing TRPC3 in myocardial cells are highly sensitive to injuries after I/R as they enhance apoptosis through increased TRPC3-mediated Ca^{2+} influx and calpain cleavage. They also demonstrated significant improvement in the viability of cardiomyocytes after SKF96365 treatment. Moreover, Meng et al. [61] observed that in vitro I/R increases TRPC6 protein expression, $[Ca^{2+}]_i$ levels, and cell apoptotic rate in a time-dependent manner in H9C2 cell line. In addition, they suggested TRPC6 as a possible target for cardioprotection in H9C2 cells since the administration of danshensu, an active component of *Salvia miltiorrhiza*, protects against I/R injury by reducing TRPC6 expression via the c-Jun N-terminal kinases (JNK) signaling pathway [61]. Hang et al. [62] also demonstrated that brain-derived neurotrophic factor (BDNF) protects against MI and inhibits H/R-mediated cardiomyocyte apoptosis through TRPC3 and TRPC6 regulation.

On the other hand, the role of TRPC1 in I/R is still unclear. A recent study suggested that it is implicated in I/R injury, as the expressions of mRNA and protein of TRPC1, Orai1, and STIM1 are significantly increased in vivo in mice subjected to myocardial I/R injury and in vitro in H9C2 cells after H/R [63]. Interestingly, the suppression of STIM1 by siRNA decreases the expression of TRPC1 and Orai1, leading to decreased intracellular Ca^{2+} accumulation and apoptosis produced by H/R in H9C2 cells [63]. Therefore, STIM1 likely regulates the expression of TRPC1 and Orai1 in the context of apoptosis and myocardial I/R injury. In contrast, Al-Awar et al. [64] speculated that TRPC1 plays a cardioprotective role against I/R injury. They showed that sitagliptin, an inhibitor of dipeptidyl peptidase-4 (DPP-4), decreases the infarct size in a rat model of I/R which correlates with the increase in protein levels of TRPC1, TRPV1, and calcitonin gene-related peptide in heart tissue. Nevertheless, a specific experiment targeting TRPC1 was not shown. Our recent study, through Western blot, confirms that TRPC1 and 6 are upregulated in a rat model of I/R although they are not inhibited by urocortin-2-mediated cardioprotection. In contrast, urocortin-2 administration in NRVM undergoing in vitro I/R inhibits SOCE and prevents I/R-induced protein overexpression of TRPC5 and Orai1 [13]. Taking into consideration these results, further investigations are necessary to clarify the functional role of TRPC channel increase after I/R.

References

1. Fabiato, A.; Fabiato, F. Excitation-contraction coupling of isolated cardiac fibers with disrupted or closed sarcolemmas. Calcium-dependent cyclic and tonic contractions. Circ. Res. 1972, 31, 293–307.
2. Bers, D.M. Cardiac excitation–contraction coupling. Nature 2002, 415, 198–205.
3. Rueda, A.; de Alba-Aguayo, D.R.; Valdivia, H.H. Ryanodine receptor, calcium leak and arrhythmias. Arch. Cardiol. Mex. 2014, 84, 191–201.
4. Falcón, D.; Galeano-Otero, I.; Calderón-Sánchez, E.; Del Toro, R.; Martín-Bórnez, M.; Rosado, J.A.; Hmadcha, A.; Smani, T. TRP Channels: Current Perspectives in the Adverse Cardiac Remodeling. Front. Physiol. 2019, 10, 159.
5. Wu, X.; Eder, P.; Chang, B.; Molkentin, J.D. TRPC channels are necessary mediators of pathologic cardiac hypertrophy. Proc. Natl. Acad. Sci. USA 2010, 107, 7000–7005.
6. Tsvilovskyy, V.V.; Zholos, A.V.; Aberle, T.; Philipp, S.E.; Dietrich, A.; Zhu, M.X.; Birnbaumer, L.; Freichel, M.; Flockerzi, V. Deletion of TRPC4 and TRPC6 in Mice Impairs Smooth Muscle Contraction and Intestinal Motility In Vivo. Gastroenterology 2009, 137, 1415–1424.
7. Noorani, M.M.Z.; Noel, R.C.; Marrelli, S.P. Upregulated TRPC3 and Downregulated TRPC1 Channel Expression during Hypertension is Associated with Increased Vascular Contractility in Rat. Front. Physiol. 2011, 2, 42.
8. Guinamard, R.; Chatelier, A.; Demion, M.; Potreau, D.; Patri, S.; Rahmati, M.; Bois, P. Functional characterization of a Ca 2+-activated non-selective cation channel in human atrial cardiomyocytes. J. Physiol. 2004, 558, 75–83.
9. Simard, C.; Sallé, L.; Rouet, R.; Guinamard, R. Transient receptor potential melastatin 4 inhibitor 9-phenanthrol abolishes arrhythmias induced by hypoxia and re-oxygenation in mouse ventricle. Br. J. Pharmacol. 2012, 165, 2354–2364.
10. Onohara, N.; Nishida, M.; Inoue, R.; Kobayashi, H.; Sumimoto, H.; Sato, Y.; Mori, Y.; Nagao, T.; Kurose, H. TRPC3 and TRPC6 are essential for angiotensin II-induced cardiac hypertrophy. EMBO J. 2006, 25, 5305–5316.
11. Ohba, T.; Watanabe, H.; Murakami, M.; Takahashi, Y.; Iino, K.; Kuromitsu, S.; Mori, Y.; Ono, K.; Iijima, T.; Ito, H. Upregulation of TRPC1 in the development of cardiac hypertrophy. J. Mol. Cell. Cardiol. 2007, 42, 498–507.
12. Domínguez-Rodríguez, A.; Ruiz-Hurtado, G.; Sabourin, J.; Gómez, A.M.; Alvarez, J.L.; Benitah, J.P. Proarrhythmic effect of sustained EPAC activation on TRPC3/4 in rat ventricular cardiomyocytes. J. Mol. Cell. Cardiol. 2015, 87, 74–78.
13. Domínguez-Rodríguez, A.; Mayoral-Gonzalez, I.; Avila-Medina, J.; de Rojas-de Pedro, E.S.; Calderón-Sánchez, E.; Díaz, I.; Hmadcha, A.; Castellano, A.; Rosado, J.A.; Benitah, J.-P.; et al. Urocortin-2 Prevents Dysregulation of Ca2+ Homeostasis and Improves Early Cardiac Remodeling After Ischemia and Reperfusion. Front. Physiol. 2018, 9, 813.
14. Yuan, J.P.; Kiselyov, K.; Shin, D.M.; Chen, J.; Shcheynikov, N.; Kang, S.H.; Dehoff, M.H.; Schwarz, M.K.; Seeburg, P.H.; Muallem, S.; et al. Homer binds TRPC family channels and is required for gating of TRPC1 by IP3 receptors. Cell 2003, 114, 777–789.
15. Adebiyi, A.; Thomas-Gatewood, C.M.; Leo, M.D.; Kidd, M.W.; Neeb, Z.P.; Jaggar, J.H. An elevation in physical coupling of type 1 inositol 1,4,5-trisphosphate (IP3) receptors to transient receptor potential 3 (TRPC3) channels constricts mesenteric arteries in genetic hypertension. Hypertension 2012, 60, 1213–1219.
16. Adebiyi, A.; Zhao, G.; Narayanan, D.; Thomas-Gatewood, C.M.; Bannister, J.P.; Jaggar, J.H. Isoform-selective physical coupling of TRPC3 channels to IP3 receptors in smooth muscle cells regulates arterial contractility. Circ. Res. 2010, 106, 1603–1612.
17. Mery, L.; Magnino, F.; Schmidt, K.; Krause, K.H.; Dufour, J.F. Alternative splice variants of hTrp4 differentially interact with the C-terminal portion of the inositol 1,4,5-trisphosphate receptors. FEBS Lett. 2001, 487, 377–383.
18. Zhang, Z.; Tang, J.; Tikunova, S.; Johnson, J.D.; Chen, Z.; Qin, N.; Dietrich, A.; Stefani, E.; Birnbaumer, L.; Zhu, M.X. Activation of Trp3 by inositol 1,4,5-trisphosphate receptors through displacement of inhibitory calmodulin from a common binding domain. Proc. Natl. Acad. Sci. USA 2001, 98, 3168–3173.
19. Trebak, M.; Lemonnier, L.; Dehaven, W.I.; Wedel, B.J.; Bird, G.S.; Putney, J.W. Complex functions of phosphatidylinositol 4,5-bisphosphate in regulation of TRPC5 cation channels. Pflugers Arch. Eur. J. Physiol. 2009, 457, 757–769.
20. Otsuguro, K.I.; Tang, J.; Tang, Y.; Xiao, R.; Freichel, M.; Tsvilovskyy, V.; Ito, S.; Flockerzi, V.; Zhu, M.X.; Zholos, A.V. Isoform-specific inhibition of TRPC4 channel by phosphatidylinositol 4,5-bisphosphate. J. Biol. Chem. 2008, 283, 10026–10036.
21. Myeong, J.; Ko, J.; Kwak, M.; Kim, J.; Woo, J.; Ha, K.; Hong, C.; Yang, D.; Kim, H.J.; Jeon, J.H.; et al. Dual action of the Gαq-PLCβ-PI(4,5)P2 pathway on TRPC1/4 and TRPC1/5 heterotetramers. Sci. Rep. 2018, 8, 12117.
22. Sabourin, J.; Robin, E.; Raddatz, E. A key role of TRPC channels in the regulation of electromechanical activity of the developing heart. Cardiovasc. Res. 2011, 92, 226–236.

23. Zhang, X.; Trebak, M. Transient receptor potential canonical 7: A diacylglycerol-activated non-selective cation channel. Handb. Exp. Pharmacol. 2014, 222, 189–204.

24. He, X.; Li, S.; Liu, B.; Susperreguy, S.; Formoso, K.; Yao, J.; Kang, J.; Shi, A.; Birnbaumer, L.; Liao, Y. Major contributio n of the 3/6/7 class of TRPC channels to myocardial ischemia/reperfusion and cellular hypoxia/reoxygenation injuries. Proc. Natl. Acad. Sci. USA 2017, 114, E4582.

25. Hofmann, T.; Obukhov, A.G.; Schaefer, M.; Harteneck, C.; Gudermann, T.; Schultz, G. Direct activation of human TRPC 6 and TRPC3 channels by diacylglycerol. Nature 1999, 397, 259–263.

26. Storch, U.; Forst, A.L.; Pardatscher, F.; Erdogmus, S.; Philipp, M.; Gregoritza, M.; Schnitzler, M.M.Y.; Gudermann, T. Dy namic NHERF interaction with TRPC4/5 proteins is required for channel gating by diacylglycerol. Proc. Natl. Acad. Sci. USA 2017, 114, E37–E46.

27. Hof, T.; Chaigne, S.; Récalde, A.; Sallé, L.; Brette, F.; Guinamard, R. Transient receptor potential channels in cardiac he alth and disease. Nat. Rev. Cardiol. 2019, 16, 344–360.

28. Ju, Y.-K.; Lee, B.H.; Trajanovska, S.; Hao, G.; Allen, D.G.; Lei, M.; Cannell, M.B. The involvement of TRPC3 channels i n sinoatrial arrhythmias. Front. Physiol. 2015, 6, 86.

29. Bush, E.W.; Hood, D.B.; Papst, P.J.; Chapo, J.A.; Minobe, W.; Bristow, M.R.; Olson, E.N.; McKinsey, T.A. Canonical tra nsient receptor potential channels promote cardiomyocyte hypertrophy through activation of calcineurin signaling. J. Bi ol. Chem. 2006, 281, 33487–33496.

30. Sunggip, C.; Shimoda, K.; Oda, S.; Tanaka, T.; Nishiyama, K.; Mangmool, S.; Nishimura, A.; Numaga-Tomita, T.; Nishid a, M. TRPC5-eNOS axis negatively regulates ATP-induced cardiomyocyte hypertrophy. Front. Pharmacol. 2018, 9, 52 3.

31. Kuwahara, K.; Wang, Y.; McAnally, J.; Richardson, J.A.; Bassel-Duby, R.; Hill, J.A.; Olson, E.N. TRPC6 fulfills a calcine urin signaling circuit during pathologic cardiac remodeling. J. Clin. Investig. 2006, 116, 3114–3126.

32. Huang, H.; Wang, W.; Liu, P.; Jiang, Y.; Zhao, Y.; Wei, H.; Niu, W. TRPC1 expression and distribution in rat hearts. Eur. J. Histochem. 2009, 53, 26.

33. Sabourin, J.; Antigny, F.; Robin, E.; Frieden, M.; Raddatz, E. Activation of transient receptor potential canonical 3 (TRP C3)-mediated Ca2+ entry by A1 adenosine receptor in cardiomyocytes disturbs atrioventricular conduction. J. Biol. Che m. 2012, 287, 26688–26701.

34. Jiang, Y.; Huang, H.; Liu, P.; Wei, H.; Zhao, H.; Feng, Y.; Wang, W.; Niu, W. Expression and localization of TRPC protei ns in rat ventricular myocytes at various developmental stages. Cell Tissue Res. 2014, 355, 201–212.

35. Ju, Y.K.; Chu, Y.; Chaulet, H.; Lai, D.; Gervasio, O.L.; Graham, R.M.; Cannell, M.B.; Allen, D.G. Store-operated Ca2+ in flux and expression of TRPC genes in mouse sinoatrial node. Circ. Res. 2007, 100, 1605–1614.

36. Numaga-Tomita, T.; Kitajima, N.; Kuroda, T.; Nishimura, A.; Miyano, K.; Yasuda, S.; Kuwahara, K.; Sato, Y.; Ide, T.; Birn baumer, L.; et al. TRPC3-GEF-H1 axis mediates pressure overload-induced cardiac fibrosis. Sci. Rep. 2016, 6, 39383.

37. Davis, J.; Burr, A.R.; Davis, G.F.; Birnbaumer, L.; Molkentin, J.D. A TRPC6-Dependent Pathway for Myofibroblast Trans differentiation and Wound Healing In Vivo. Dev. Cell 2012, 23, 705–715.

38. Rose, R.A.; Hatano, N.; Ohya, S.; Imaizumi, Y.; Giles, W.R. C-type natriuretic peptide activates a non-selective cation c urrent in acutely isolated rat cardiac fibroblasts via natriuretic peptide C receptor-mediated signalling. J. Physiol. 2007, 580, 255–274.

39. Harada, M.; Luo, X.; Qi, X.Y.; Tadevosyan, A.; Maguy, A.; Ordog, B.; Ledoux, J.; Kato, T.; Naud, P.; Voigt, N.; et al. Tran sient receptor potential canonical-3 channel-dependent fibroblast regulation in atrial fibrillation. Circulation 2012, 126, 2 051–2064.

40. Ikeda, K.; Nakajima, T.; Yamamoto, Y.; Takano, N.; Tanaka, T.; Kikuchi, H.; Oguri, G.; Morita, T.; Nakamura, F.; Komuro, I. Roles of transient receptor potential canonical (TRPC) channels and reverse-mode Na+/Ca2+ exchanger on cell proli feration in human cardiac fibroblasts: Effects of transforming growth factor β1. Cell Calcium 2013, 54, 213–225.

41. Zhang, Y.-H.; Wu, H.-J.; Che, H.; Sun, H.-Y.; Cheng, L.-C.; Li, X.; Au, W.-K.; Tse, H.-F.; Li, G.-R. Functional transient rec eptor potential canonical type 1 channels in human atrial myocytes. Pflugers Arch. 2013, 465, 1439–1449.

42. Hofmann, T.; Schaefer, M.; Schultz, G.; Gudermann, T. Subunit composition of mammalian transient receptor potential channels in living cells. Proc. Natl. Acad. Sci. USA 2002, 99, 7461–7466.

43. Oda, S.; Numaga-Tomita, T.; Kitajima, N.; Toyama, T.; Harada, E.; Shimauchi, T.; Nishimura, A.; Ishikawa, T.; Kumagai, Y.; Birnbaumer, L.; et al. TRPC6 counteracts TRPC3-Nox2 protein complex leading to attenuation of hyperglycemia-ind uced heart failure in mice. Sci. Rep. 2017, 7, 7511.

44. Doleschal, B.; Primessnig, U.; Wölkart, G.; Wolf, S.; Schernthaner, M.; Lichtenegger, M.; Glasnov, T.N.; Kappe, C.O.; M ayer, B.; Antoons, G.; et al. TRPC3 contributes to regulation of cardiac contractility and arrhythmogenesis by dynamic i nteraction with NCX1. Cardiovasc. Res. 2015, 106, 163–173.

45. Goel, M.; Zuo, C.D.; Sinkins, W.G.; Schilling, W.P. TRPC3 channels co-localize with the Na+, Ca2+ exchanger and the Na+ pump in the axial component of the transverse-axial-tubular system (TATS) of rat ventricle. Am. J. Physiol. Heart C irc. Physiol. 2006, 292, H874–H883.

46. Lemonnier, L.; Trebak, M.; Lievremont, J.P.; Bird, G.S.; Putney, J.W. Protection of TRPC7 cation channels from calcium inhibition by closely associated SERCA pumps. FASEB J. 2006, 20, 503–505.

47. Gees, M.; Colsoul, B.; Nilius, B. The role of transient receptor potential cation channels in Ca2+ signaling. Cold Spring Harb. Perspect. Biol. 2010, 2, a003962.

48. Qu, Y.; Boutjdir, M. TRPC channels, an overarching Ca(2+) paradigm in the developing heart. Cardiovasc. Res. 2011, 9 2, 189–190.

49. Abramowitz, J.; Birnbaumer, L. Physiology and pathophysiology of canonical transient receptor potential channels. FAS EB J. 2009, 23, 297–328.

50. Chen, J.; Crossland, R.F.; Noorani, M.M.Z.; Marrelli, S.P.; Marrelli, S.P. Inhibition of TRPC1/TRPC3 by PKG contributes to NO-mediated vasorelaxation. Am. J. Physiol. Heart Circ. Physiol. 2009, 297, 417–424.

51. Jardin, I.; Gómez, L.J.; Salido, G.M.; Rosado, J.A. Dynamic interaction of hTRPC6 with the Orai1-STIM1 complex or hT RPC3 mediates its role in capacitative or non-capacitative Ca2+ entry pathways. Biochem. J. 2009, 420, 267–276.

52. Bröker-Lai, J.; Kollewe, A.; Schindeldecker, B.; Pohle, J.; Nguyen Chi, V.; Mathar, I.; Guzman, R.; Schwarz, Y.; Lai, A.; Weißgerber, P.; et al. Heteromeric channels formed by TRPC 1, TRPC 4 and TRPC 5 define hippocampal synaptic tran smission and working memory. EMBO J. 2017, 36, 2770–2789.

53. Goel, M.; Sinkins, W.G.; Schilling, W.P. Selective association of TRPC channel subunits in rat brain synaptosomes. J. B iol. Chem. 2002, 277, 48303–48310.

54. Zhou, R.; Hang, P.; Zhu, W.; Su, Z.; Liang, H.; Du, Z. Whole Genome Network Analysis of Ion Channels and Connexins in Myocardial Infarction. Cell. Physiol. Biochem. 2011, 27, 299–304.

55. Makarewich, C.A.; Zhang, H.; Davis, J.; Correll, R.N.; Trappanese, D.M.; Hoffman, N.E.; Troupes, C.D.; Berretta, R.M.; Kubo, H.; Madesh, M.; et al. Transient receptor potential channels contribute to pathological structural and functional re modeling after myocardial infarction. Circ. Res. 2014, 115, 567–580.

56. Jung, C.; Gené, G.G.; Tomás, M.; Plata, C.; Selent, J.; Pastor, M.; Fandos, C.; Senti, M.; Lucas, G.; Elosua, R.; et al. A gain-of-function SNP in TRPC4 cation channel protects against myocardial infarction. Cardiovasc. Res. 2011, 91, 465–471.

57. Shan, D.; Marchase, R.B.; Chatham, J.C. Overexpression of TRPC3 increases apoptosis but not necrosis in response t o ischemia-reperfusion in adult mouse cardiomyocytes. Am. J. Physiol. Cell Physiol. 2008, 294, C833–C841.

58. Kojima, A.; Fukushima, Y.; Ito, Y.; Ding, W.-G.; Kitagawa, H.; Matsuura, H. Transient Receptor Potential Canonical Cha nnel Blockers Improve Ventricular Contractile Functions After Ischemia/Reperfusion in a Langendorff-perfused Mouse Heart Model. J. Cardiovasc. Pharmacol. 2018, 71, 248–255.

59. Parekh, A.B.; Putney, J.W. Store-operated calcium channels. Physiol. Rev. 2005, 85, 757–810.

60. Liu, H.; Yang, L.; Chen, K.-H.; Sun, H.-Y.; Jin, M.-W.; Xiao, G.-S.; Wang, Y.; Li, G.-R. SKF-96365 blocks human ether-à-go-go-related gene potassium channels stably expressed in HEK 293 cells. Pharmacol. Res. 2016, 104, 61–69.

61. Meng, Y.; Li, W.-Z.; Shi, Y.-W.; Zhou, B.-F.; Ma, R.; Li, W.-P. Danshensu protects against ischemia/reperfusion injury an d inhibits the apoptosis of H9c2 cells by reducing the calcium overload through the p-JNK-NF-κB-TRPC6 pathway. Int. J. Mol. Med. 2016, 37, 258–266.

62. Hang, P.; Zhao, J.; Cai, B.; Tian, S.; Huang, W.; Guo, J.; Sun, C.; Li, Y.; Du, Z. Brain-derived neurotrophic factor regulat es TRPC3/6 channels and protects against myocardial infarction in rodents. Int. J. Biol. Sci. 2015, 11, 536–545.

63. He, F.; Wu, Q.; Xu, B.; Wang, X.; Wu, J.; Huang, L.; Cheng, J. Suppression of Stim1 reduced intracellular calcium conc entration and attenuated hypoxia/reoxygenation induced apoptosis in H9C2 cells. Biosci. Rep. 2017, 37, BSR2017124 9.

64. Al-Awar, A.; Almási, N.; Szabó, R.; Takacs, I.; Murlasits, Z.; Szűcs, G.; Török, S.; Pósa, A.; Varga, C.; Kupai, K. Novel P otentials of the DPP-4 Inhibitor Sitagliptin against Ischemia-Reperfusion (I/R) Injury in Rat Ex-Vivo Heart Model. Int. J. Mol. Sci. 2018, 19, 3226.